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(54) Title: ASYMETRIC HYDROGENATION OF $\beta$ - or $\gamma$ -KETOESTERS AND $\beta$ - or $\gamma$ -KETOAMIDES			
(57) Abstract  $\beta$ - or $\gamma$ -Ketoesters and $\beta$ - or $\gamma$ -ketoamides are asymmetrically reduced with a Ru(II)-BINAP derived catalyst at about 40 °C and about 50 N/mm <sup>2</sup> of hydrogen in the presence of a strong acid.			

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**TITLE OF THE INVENTION****ASYMMETRIC HYDROGENATION OF  $\beta$ - or  $\gamma$ -KETOESTERS AND  $\beta$ - or  $\gamma$ -KETOAMIDES****5 SUMMARY OF THE INVENTION**

This is a continuation in part of copending application Ser. No. 07/922,355 filed 13 July 1992.

The present invention relates to a novel process in which it has been shown that in the presence of trace amounts of strong acid an  
10 asymmetric hydrogenation proceeds at low temperatures and readily attainable pressures with substrate/catalyst ratios up to about 10,000. The reaction can be carried out at pressures of less than or equal to 150 psi as such the reaction does not require special equipment to run the reaction and can be carried out on a pilot plant scale.

15 Another aspect of this invention is a simple reproducible procedure for preparation of purified catalyst. This invention also relates to the identification of the catalyst responsible for carrying out this process.

**20 BACKGROUND OF THE INVENTION**

Asymmetric hydrogenation using the Ru(II)-BINAP or Ru(II)-t-BINAP system (Ruthenium Complexes of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl) introduced by Noyori, et al. provides high enantioselectivity  
25 over a wide range of substrates with remarkable turnover (Noyori et al. Acc. Chem. Res., 23, 345 (1990)). However, all reports concerning the reduction of  $\beta$ -ketoesters (Noyori et al., J. Am. Chem. Soc. 109, 5856 (1987)) suffer from the need for temperatures greater than 80°C or hydrogen pressures greater than 6895 N/mm<sup>2</sup> where special apparatus  
30 is required (Kitamura et al., Tetrahedron Lett., 32, 4163 (1991); Taber et al, Tetrahedron Lett., 32, 4227 (1991); Keck et al, J. Org. Chem., 56, 6606(1991)).

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**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1.

250 MHz  $^1\text{H}$  NMR of  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{R})\text{-BINAP})_2]^- \cdot \text{CH}_3\text{Ph}$  in  $\text{CD}_2\text{Cl}_2$  at room temperature.

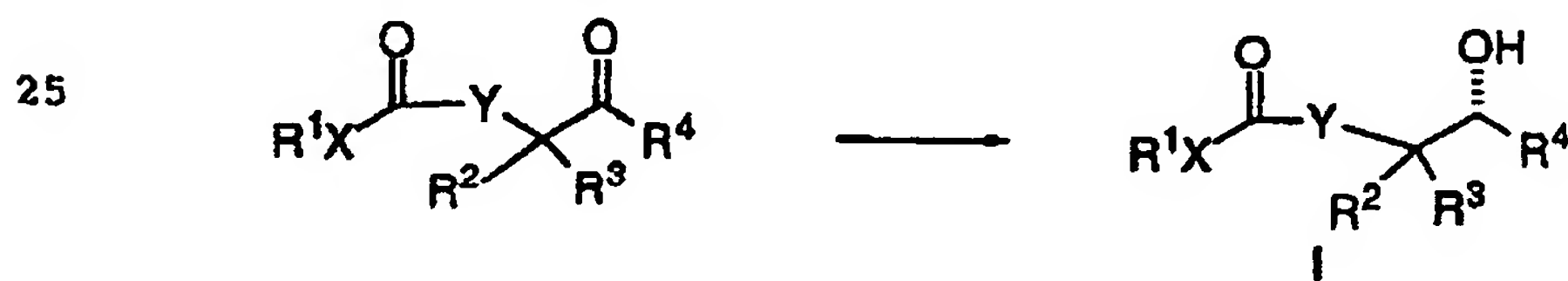
Figure 2.

Expansion of the 3.0 ppm to 3.5 ppm region of 400.13 MHz  $^1\text{H}$  NMR of  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{R})\text{-BINAP})_2]^- \cdot \text{CH}_3\text{Ph}$  in  $\text{CD}_2\text{Cl}_2$  at  $-40^\circ\text{C}$ .

(a) is the fully coupled spectrum of this region; (b) is the decoupled spectrum of this region resulting from the irradiation of the peak at 8.53 ppm; and (c) is the decoupled spectrum of this region resulting from the irradiation of the peak at 1.41 ppm.

**DETAILED DESCRIPTION OF THE INVENTION**

The novel process for the asymmetric reduction of  $\beta$ - or  $\gamma$ -ketoesters and  $\beta$ - or  $\gamma$ -ketoamides comprises adding a chiral ruthenium BINAP or t-BINAP catalyst, for example  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{S})\text{-BINAP})_2]^-$ ,  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{S})\text{-t-BINAP})_2]^-$ ,  $[\text{RuCl}(\text{PhH})(\text{BINAP})]\text{Cl}$  or  $[\text{RuCl}(\text{PhH})(\text{t-BINAP})]\text{Cl}$  catalyst to a solution of the  $\beta$ - or  $\gamma$ -ketoesters and  $\beta$ - or  $\gamma$ -ketoamides in a C1-3 alkanol, preferably methanol, followed by the addition of a strong acid and reducing the  $\beta$ - or  $\gamma$ -ketoesters and  $\beta$ - or  $\gamma$ -ketoamides by agitation in the presence of hydrogen.



wherein:

30  $\text{R}^1$  is straight or branched C1-C4 alkyl;

X is O or  $\text{NR}^5$ ;

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Y is  $C(R^2)_2$  or a single bond;


R<sup>2</sup> is: H, or straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

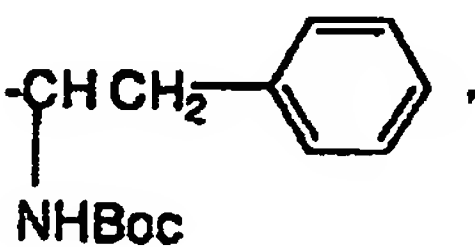
5 R<sup>3</sup> is: H, straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl, CH<sub>2</sub>NHCOR<sup>6</sup>, or R<sup>1</sup> and R<sup>3</sup> taken together form a lactone or cyclic amide of 5 to 7 atoms one of which is an oxygen or nitrogen;

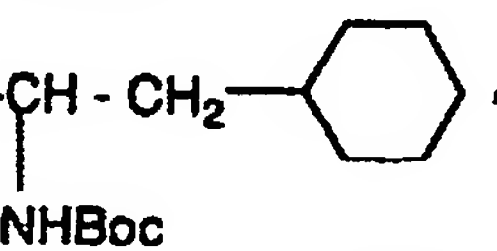
R<sup>4</sup> is:

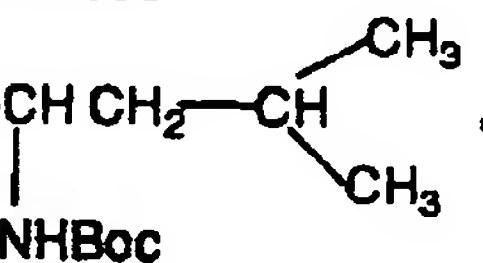
(a) CH<sub>3</sub>,

(b) CH<sub>2</sub>Cl,

(c) CH<sub>2</sub>OCH<sub>2</sub>--OCH<sub>3</sub>,

(d) ,

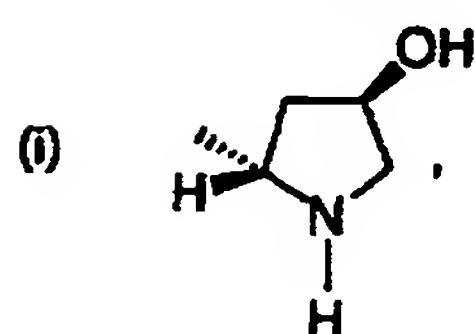
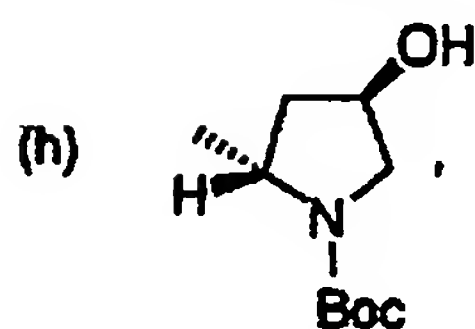
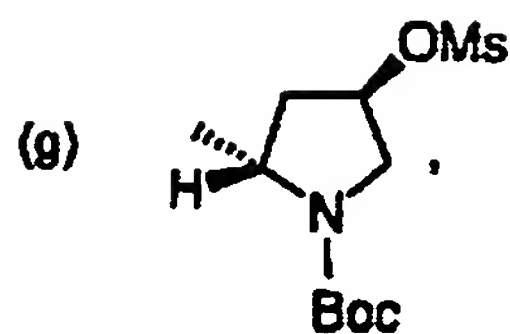
(e) ,

(f) ,

25

30

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R<sup>3</sup> and R<sup>4</sup> taken together form a ring of 5 to 7 carbons, in which  
R<sup>3</sup> and R<sup>4</sup> represent a carbon chain of 3 to 5 carbons;

R<sup>5</sup> is H, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or CO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl;  
and

R<sup>6</sup> is straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or O-C<sub>1</sub>-C<sub>4</sub> alkyl,  
phenyl, O-benzyl.

#### Abbreviations

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

t-BINAP 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl

BINAP in the instant application represents all chiral ligands

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of 2,2'-bis(diarylphosphino)-1,1'-binaphthyl and it is understood that although the specific stereochemistry is not recited that the ligand utilized is either the R- or the S-antipode. The selection of the R- or the S-BINAP ligand will determine the stereochemistry of the  $\beta$ - or  $\gamma$ -hydroxyesters and  $\beta$ - or  $\gamma$ -hydroxyamides produced.

\* The asterik is being used to represent a specific enantiomer which is dependent on the stereochemistry of the BINAP employed.

1 N/mm<sup>2</sup> is equivalent to approximately 0.145 psi

Boc t-butyloxycarbonyloxy

Ms methanesulfonyl

COD Cyclooctadienyl

om overlapping multiplet

The amount of catalyst relative to amount of substrate over about 0.02 mole % is not critical, and excess catalyst will not seriously effect yield and enantiomeric purity, but amounts up to about 0.1 mole % are quite adequate.

The concentration of substrate in the alkanol is preferably about 0.5 to about 2.25 M although the concentration is not critical. It is preferred that the alkanol solvent be deoxygenated before reduction such as by flowing nitrogen for several minutes.

The strong acid used in the novel process is about 0.1 to 10 mole % of HCl, H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub>, CH<sub>3</sub>SO<sub>3</sub>H, or the like, preferably HCl, H<sub>2</sub>SO<sub>4</sub>, or CH<sub>3</sub>SO<sub>3</sub>H.

The reaction mixture is agitated by shaking or stirring and the reduction is accomplished at about 40-50°C and a hydrogen pressure of about 50 to about 1400 N/mm<sup>2</sup> until the required hydrogen uptake has occurred, usually in about 3-8 hours. Under the above-described conditions an enantiomeric excess >97% is routinely achieved for an



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achiral starting  $\beta$  or  $\gamma$ -ketoester and  $\beta$  or  $\gamma$ -ketoamide and the reaction is diastereoselective when the starting  $\beta$ - or  $\gamma$ -ketoester and  $\beta$ - or  $\gamma$ -ketoamide is chiral.

There is a dramatic dependence of the reaction on low levels of strong acid. A reaction mixture of a  $\beta$ - or  $\gamma$ -ketoester, or a  $\beta$ - or  $\gamma$ -ketoamide and catalyst, containing no acid, was exposed at 345 N/mm<sup>2</sup> (50 psi) of hydrogen at 50°C for 24 hours with no hydrogen uptake. When 1 mole % HCl was added, the reaction went to completion in 3 hours. Sulfuric acid was equally effective. Significantly, the catalyst [RuCl(PhH)((R)-BINAP)]Cl, which contains no endogenous amine, also shows this acid dependence. A very low concentration of acid after neutralization of any basic impurities is required for maximum reaction rate. Any further increase in acid concentration provides no rate enhancement.

The catalyst is easily prepared using standard anaerobic techniques from commercially available (cyclooctadiene)ruthenium dichloride. Filtration of the product using a double ended filter provides a pure product, [(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NH<sub>2</sub>]<sup>+</sup>[Ru<sub>2</sub>Cl<sub>5</sub>(BINAP)<sub>2</sub>]<sup>-</sup> as a solvate, such as, benzene, toluene, xylene, chlorobenzene, or 1,2-, 1,3-, or 1,4-dichlorobenzene, etc.

Asymmetric reduction of a  $\beta$ -ketoester to the corresponding enantiomerically pure  $\beta$ -hydroxyester is an important synthetic step in the synthesis of a number of important useful chemical products such as:

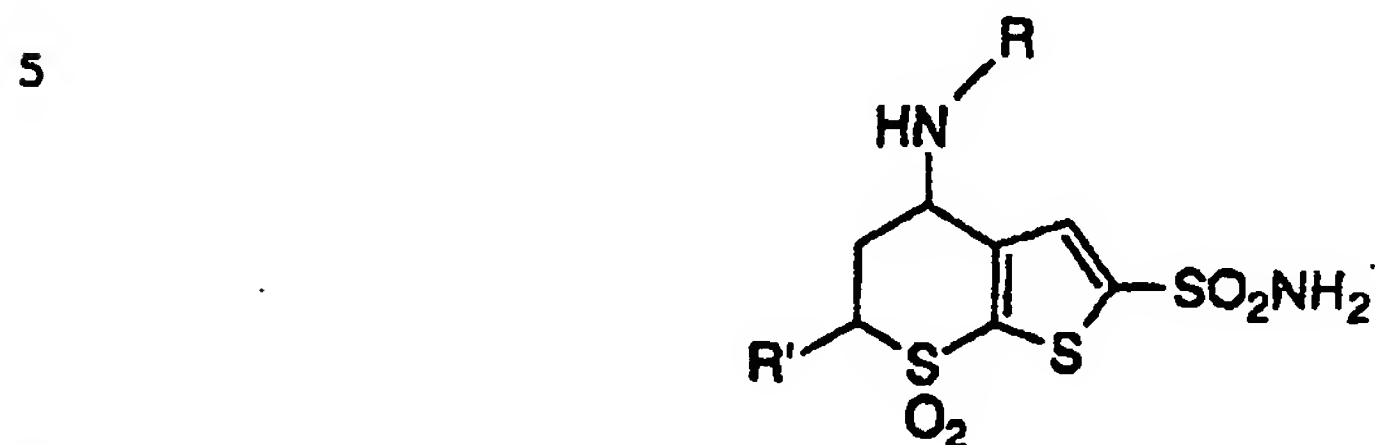
1. The immunosuppressive agent, FK-506 (Jones et al. J. Org. Chem., **54**, 17-19 (1989));
2. Colletal (Keck et al., J. Org. Chem., **56**, 6606-6611 (1991));
3. Carnitine (Tetrahedron Letters, **29**, 1555-1556 (1988));
4. Statine (Nishi et al., Tetrahedron Letters, **29**, 6327-6330 (1988));
5. Gleosporine (Schreiber et al., J. Amer. Chem. Soc., **110**, 6210-6218 (1988)).

Another important type of product involving an asymmetric reduction of a  $\beta$ -ketoester in its synthesis is a group of



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carbomic anhydrase inhibitors which are topically effective in the treatment of ocular hypertension and glaucoma associated therewith. This class of compounds has the general structure:



or a pharmaceutically acceptable salt thereof, wherein R is C<sub>1</sub>-5 alkyl; and R<sup>1</sup> is hydrogen, C<sub>1</sub>-3 alkyl or C<sub>1</sub>-3 alkoxy-C<sub>1</sub>-3 alkyl and are disclosed in U.S. Patent No. 4,797,413, issued January 10, 1989. The series of steps in the synthesis depicted below for the topical carbomic anhydrase inhibitor, wherein R is defined as n-propyl and R' is defined as methoxypropyl, is representative of the process of this invention.

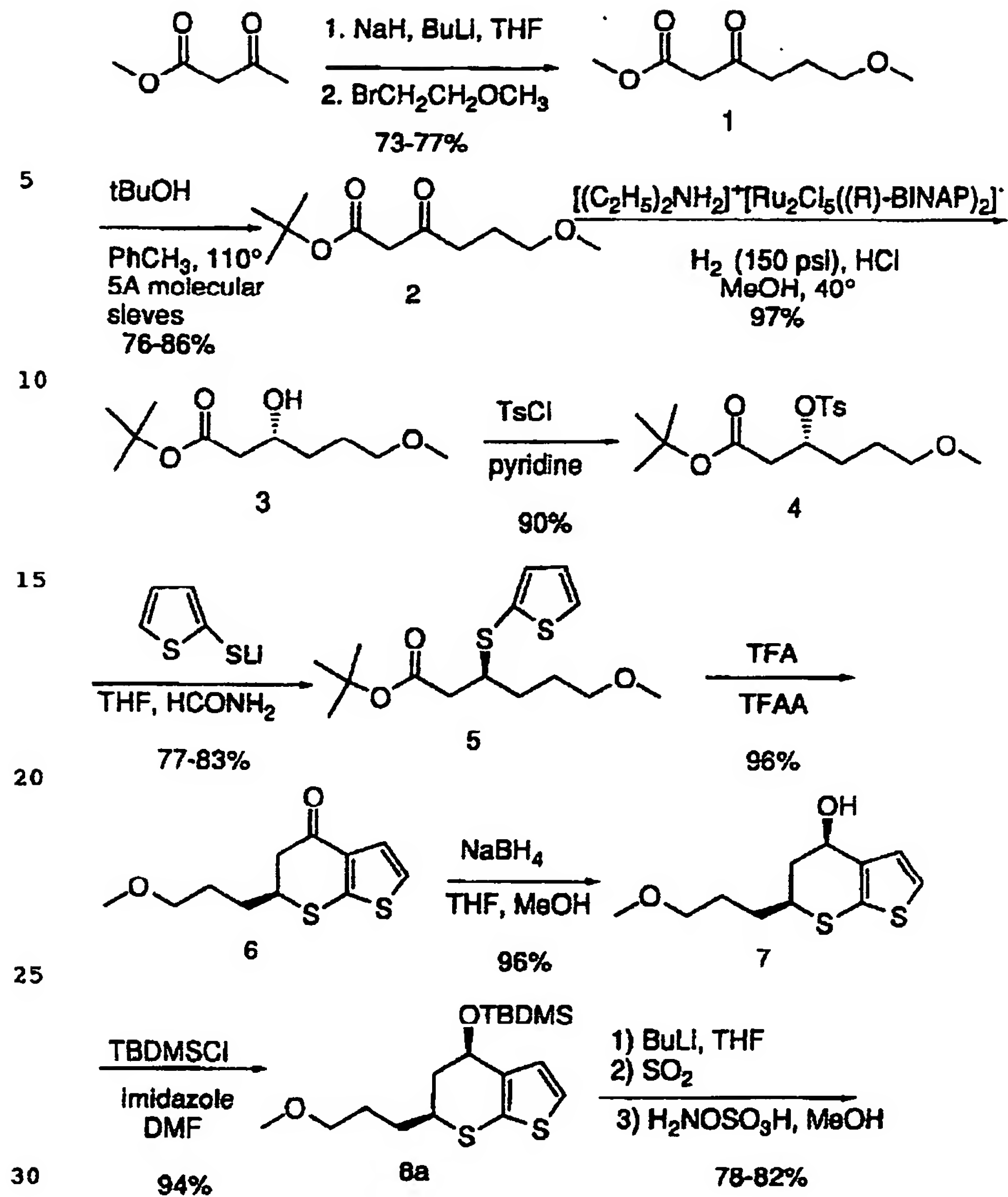
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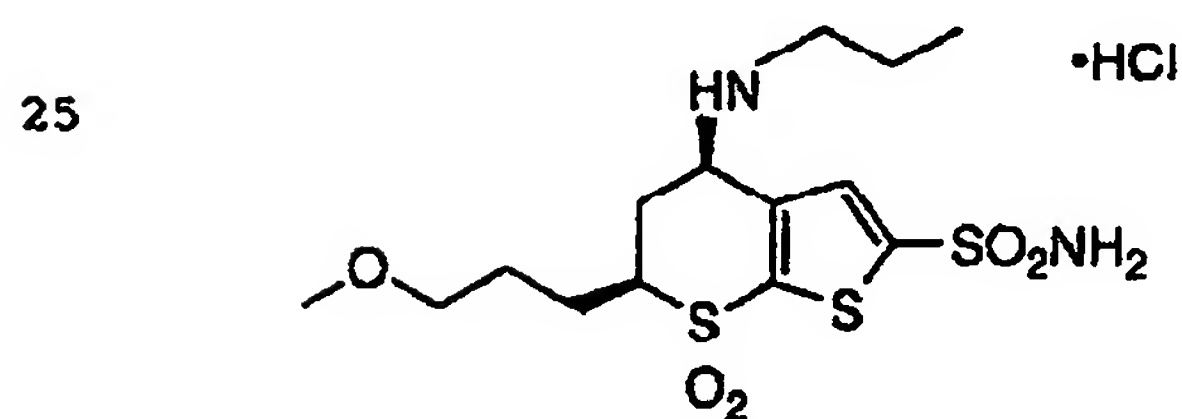
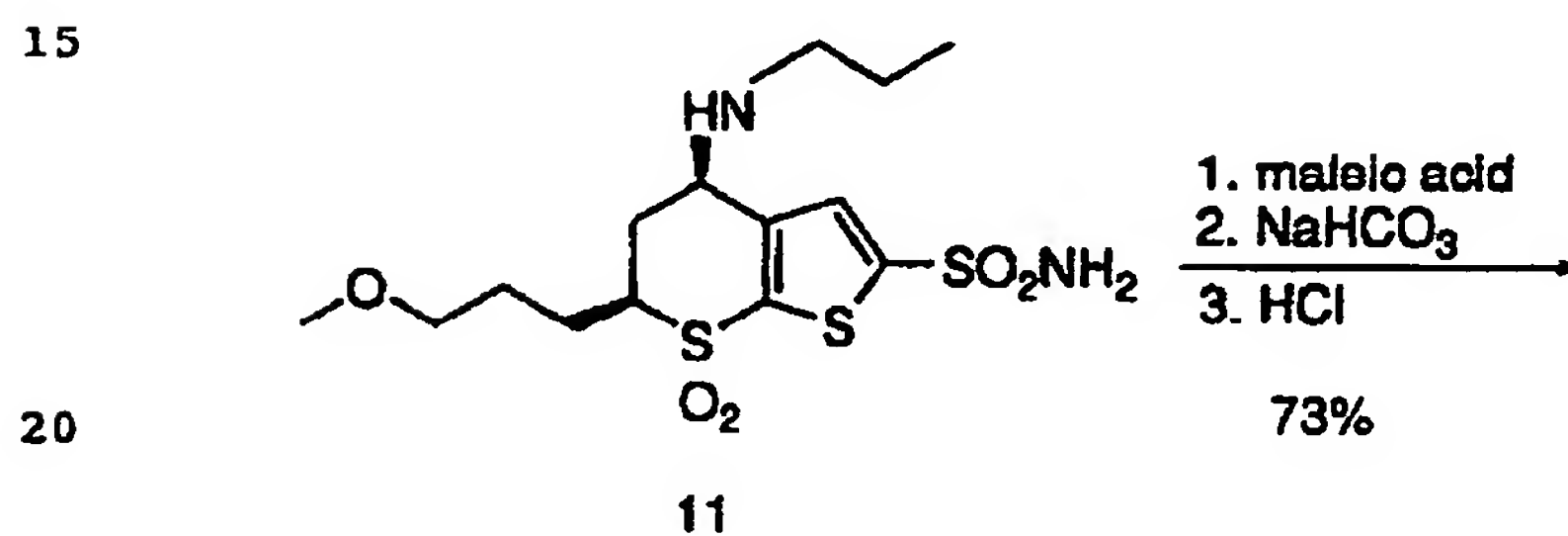
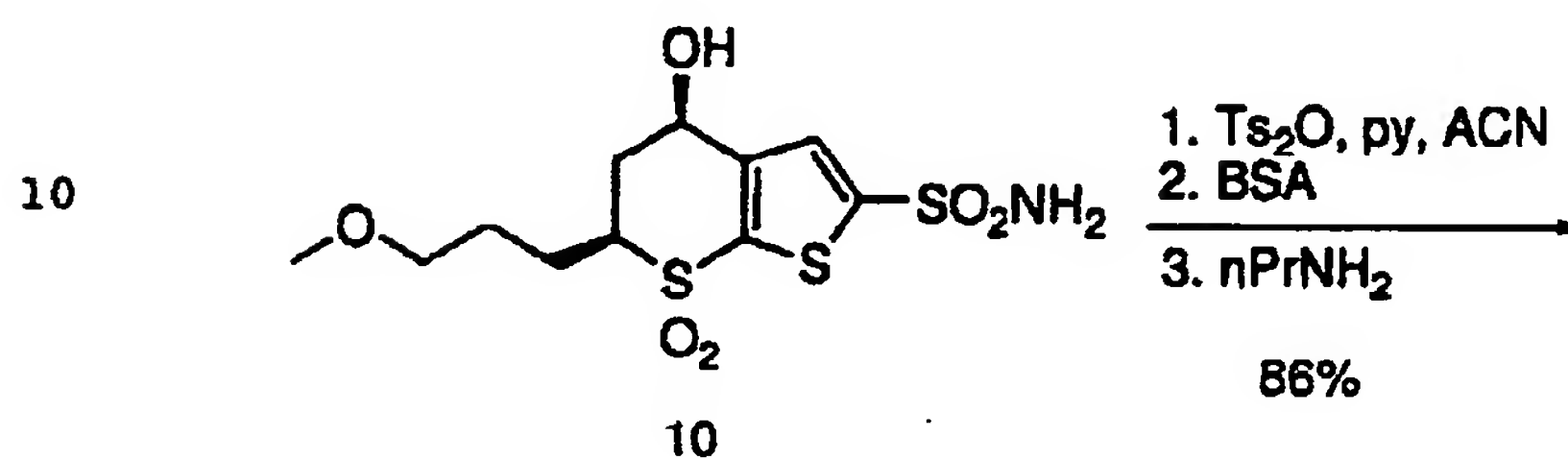
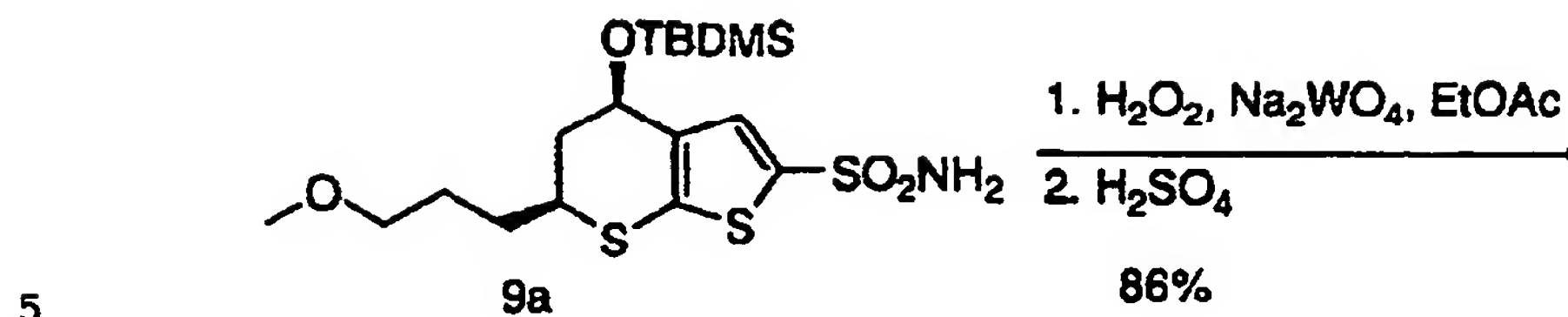
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- 9 -



30

The novel process of this invention is depicted as 2 → 3 in the above reaction scheme. The enantiomerically pure alcohol produced in this step is responsible for installing the optical activity of the carbonic anhydrase inhibitors. Its activation and displacement with

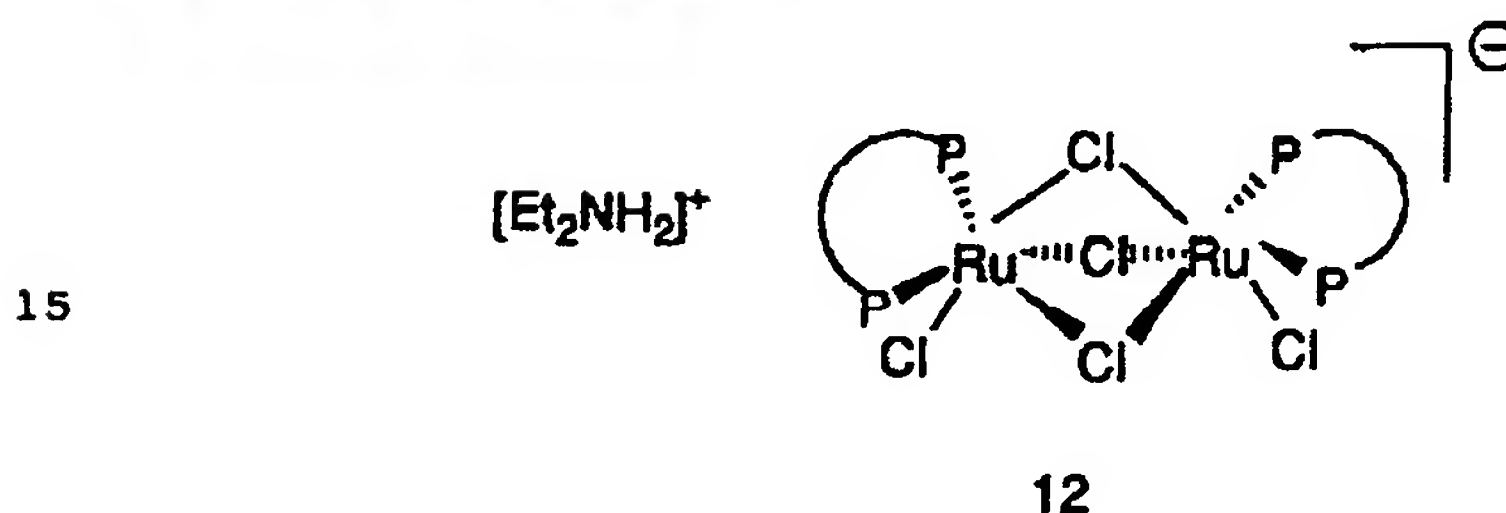
- 10 -

inversion provides the optically pure 5 which can be cyclized to the key intermediate 6 which contains the carbon skeleton of these compounds.

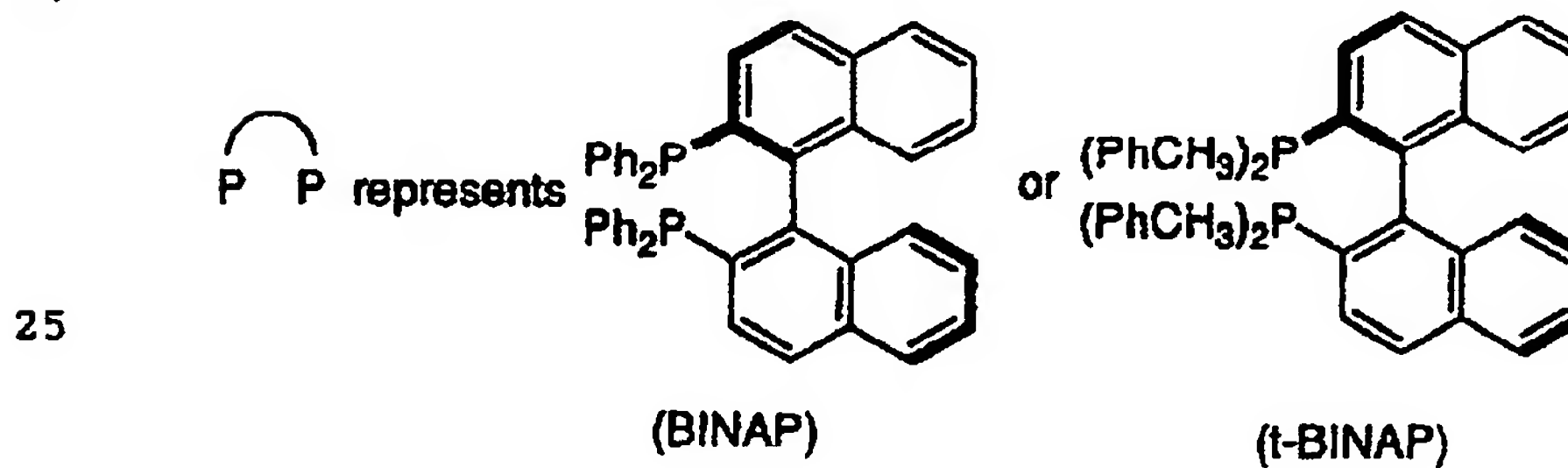
The following examples further illustrate the use of the process for the preparation of the compounds of Formula I and the use of this catalyst in this process and, as such, are not be considered or construed as limiting the invention recited in the appended claims.

### EXAMPLE 1

#### 10 Catalyst Preparation



20



30 Step A: Preparation of  $[(C_2H_5)_2NH_2]^+[Ru_2Cl_5((R)-BINAP)_2]^-$   
 $\cdot CH_3Ph$  Structure 12

(Cyclooctadienyl)ruthenium dichloride (214 mg, 0.76 mmol) and (R)-BINAP (500 mg, 0.80 mmol) were placed in a 50 mL round bottom flask and connected to a double ended filter (Kontes #215500-6044) with a 100 mL round bottom flask at the opposite end.

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Vacuum grease was used to ensure an air-tight seal. Rubber bands were a simple and effective way of holding the apparatus together. The entire apparatus was evacuated and filled with nitrogen. Dry toluene (17 mL) and dry triethylamine (1.7 mL), which had been deoxygenated with flowing nitrogen for several minutes, were added via the lower side arm. The vessel was sealed and the mixture heated to 140°C producing a deep brick red colored solution. After 4 hours the apparatus was allowed to cool to room temperature with vigorous stirring while the catalyst precipitated. The apparatus was vented to nitrogen and inverted to filter the product using vacuum on the lower side arm and nitrogen on the upper. The precipitate was washed with deoxygenated toluene (17 mL), and the flask containing the filtrate was exchanged for an empty one. (<sup>31</sup>P NMR showed that the filtrate contained none of the desired product.) The entire apparatus was put under vacuum and the product was dried overnight to give 470 mg (75%) of a dark red solid:

<sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400.13 MHz) δ 8.53(br s, 2H), 8.07 (t, J=8.8 Hz, 4H), 7.82 (t, J=8.3 Hz, 2H), 7.65 (m, 6H), 7.55 (m, 4H), 7.47 (m, 4H), 7.4-7.1 (m, 18H), 6.95 (m, 2H), 6.84 (t, J=7.4 Hz, 2H), 6.8-6.7 (om, 4H), 6.7-6.6 (om, 4H), 6.6-6.5 (om, 12H), 3.24 (br m, 6H), 2.3 (s, 3H), 1.45 (t, J=7.3 Hz, 9H) [See figure 1 for <sup>1</sup>H NMR spectrum]; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 161.98 MHz) δ 56.5 (d, J=38.0 Hz), 52.3 (d, J=38.0 Hz);

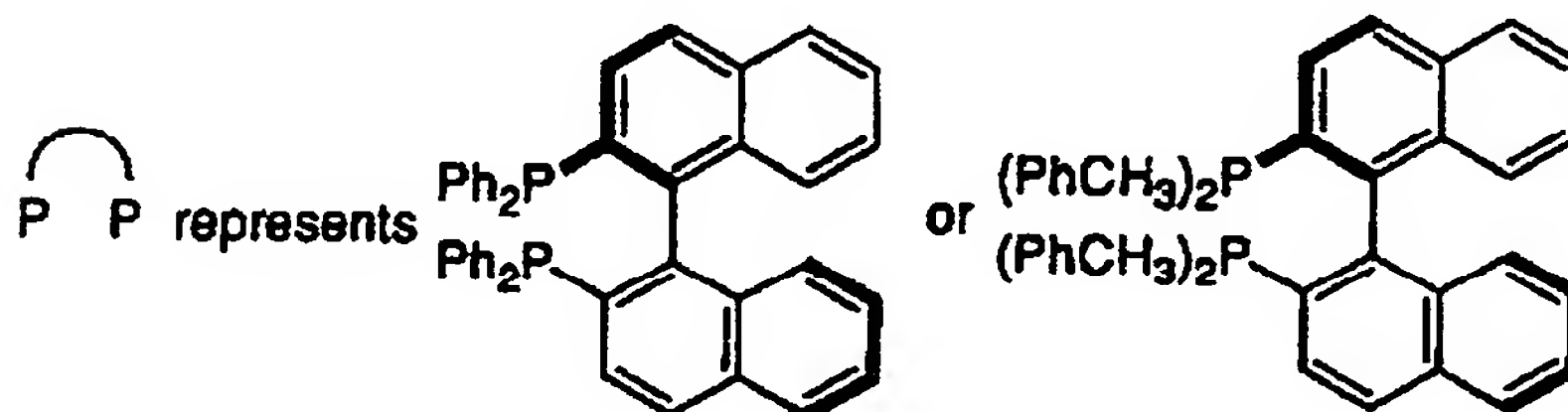
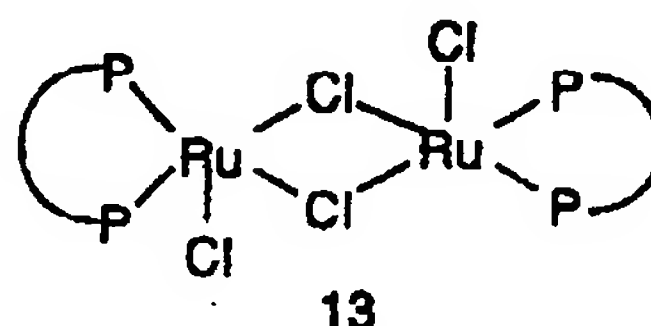
Analysis Calc'd for C<sub>99</sub>H<sub>84</sub>Cl<sub>5</sub>NP<sub>4</sub>Ru<sub>2</sub>:

	C 66.39, H 4.73, N 0.78, Cl 9.90, P 6.92;
25 Found	C 66.06, H 4.74, N 0.74, Cl 9.79, P 6.91.

Decoupling and spiking experiments unequivocally established the presence of diethylammonium ion. At -40°C the methylene protons of the diethylammonium appear as two multiplets at 3.2 ppm. [See figure 2 (a) for <sup>1</sup>H NMR spectrum] When the triplet at 1.4 ppm was irradiated the signal at 3.2 ppm appears as two doublets of triplets. [See figure 2 (c) for <sup>1</sup>H NMR spectrum] When the broad singlet at 8.53 ppm is irradiated the signal at 3.2 ppm appears as two doublets of quartets. [See figure 2 (b) for <sup>1</sup>H NMR spectrum]. When

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diethylamine was added to the solution the signal at 3.2 ppm was seen to coalesce with the diethylamine signal. Triethylamine did not produce this behavior.



20 **Step B: Preparation of  $\text{Ru}_2\text{Cl}_4((R)\text{-BINAP})_2$  Structure 13**

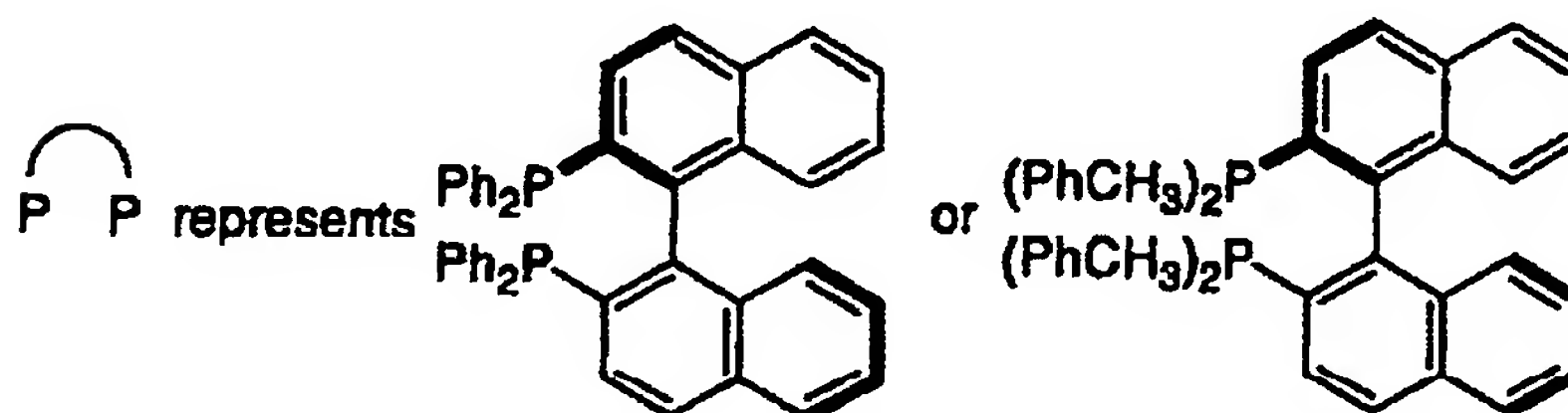
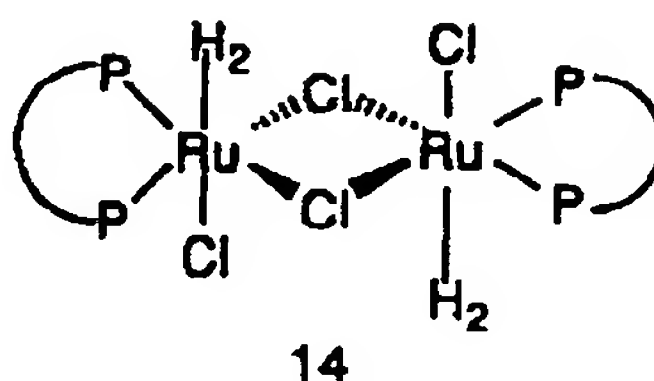
The catalyst 12 (12 mg, 6.7  $\mu\text{mol}$ ) was loaded into a gas tight NMR tube (available from Wilmad) which was evacuated and refilled with nitrogen. Dry methylene chloride- $d_2$  (0.8 mL) was deoxygenated by bubbling with nitrogen for 2 minutes. It was added with a thin needle by partially unstoppering the tube while nitrogen was

25 flowing through the plug, flushing air away from its mouth. The atmosphere over the solvent was immediately purged by carefully evacuating and refilling with nitrogen. Catalyst dissolution was aided by the use of sonication or a vortex mixer. Methanesulfonic acid (4  $\mu\text{L}$ , 62  $\mu\text{mol}$ ) was added to give the desired product:

30  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 400.13 MHz)  $\delta$  8.14 (d,  $J=7.9$  Hz, 2H), 8.10 (d,d,  $J=9.1, 1.6$  Hz, 2H), 7.73 (d,  $J=7.9$  Hz, 2H), 7.65 (t,  $J=7.5$  Hz, 2H), 7.59 (m, 2H), 7.55-7.35 (om, 22H), 7.26-7.09 (om, 18H), 6.82-6.77 (om, 4H), 6.15 (m, 4H), 6.05 (d,  $J=8.7$  Hz, 2H), 5.83 (dd,  $J=12.3, 7.9$  Hz,

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4H);  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 161.98 MHz)  $\delta$  62.6 (d,  $J=40.3$  Hz), 13.7 (d,  $J=40.3$  Hz).



**Step C: Preparation of  $[\text{Ru}_2\text{Cl}_4((R)\text{-BINAP})_2(\text{H}_2)_2]$  Structure 14**

A gas tight NMR tube containing 13 was put under a  
 20 hydrogen atmosphere by evacuating and filling with hydrogen at a  
 positive pressure of 8 psi. To ensure saturation of the solution, the tube  
 was put on a vortex mixer while attached to the manifold and stirred for  
 10 minutes.

The  $^1\text{H}$  and  $^{31}\text{P}$  spectra indicate that the hydrogen adduct is  
 25 a mixture of conformational or configurational forms.

$^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 400.13 MHz)  $\delta$  8.2-5.8 (om), -9.85, -10.08, -10.2,  
 -10.88, -11.12, -11.52;  $^{31}\text{P}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 161.98 MHz)  $\delta$  58.8 (d,  
 $J=29.7$  Hz), 56.2 (d,  $J=30.4$  Hz), 55.1 (d,  $J=32.4$  Hz), 54.9 (d,  $J=31.7$   
 Hz), 51.7 (d,  $J=29.7$  Hz), 50.9 (d,  $J=31.0$  Hz), 50.5 (d,  $J=33.1$  Hz), 48.5  
 30 (d,  $J=31.7$  Hz), 47.2 (d,  $J=30.4$  Hz), 46.7 (d,  $J=33.1$  Hz), 46.4 (d,  
 $J=32.4$  Hz), 44.9 (d,  $J=31.0$  Hz).

The species 13 and 14 have been shown to be active  
 catalysts as demonstrated in the following experiment:



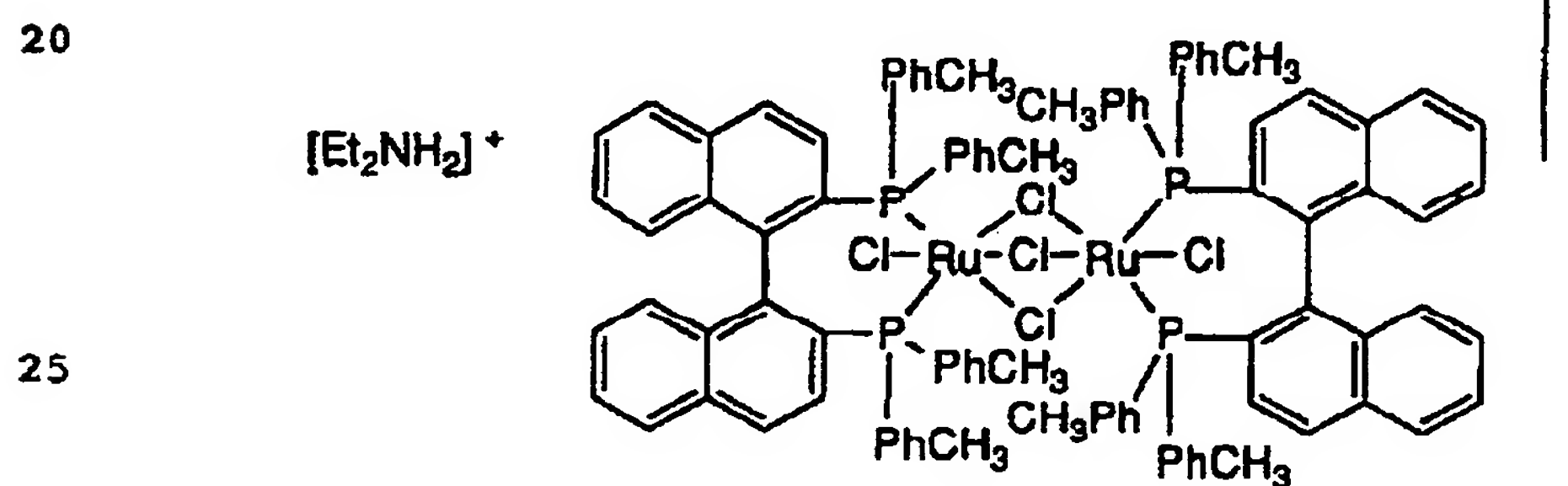
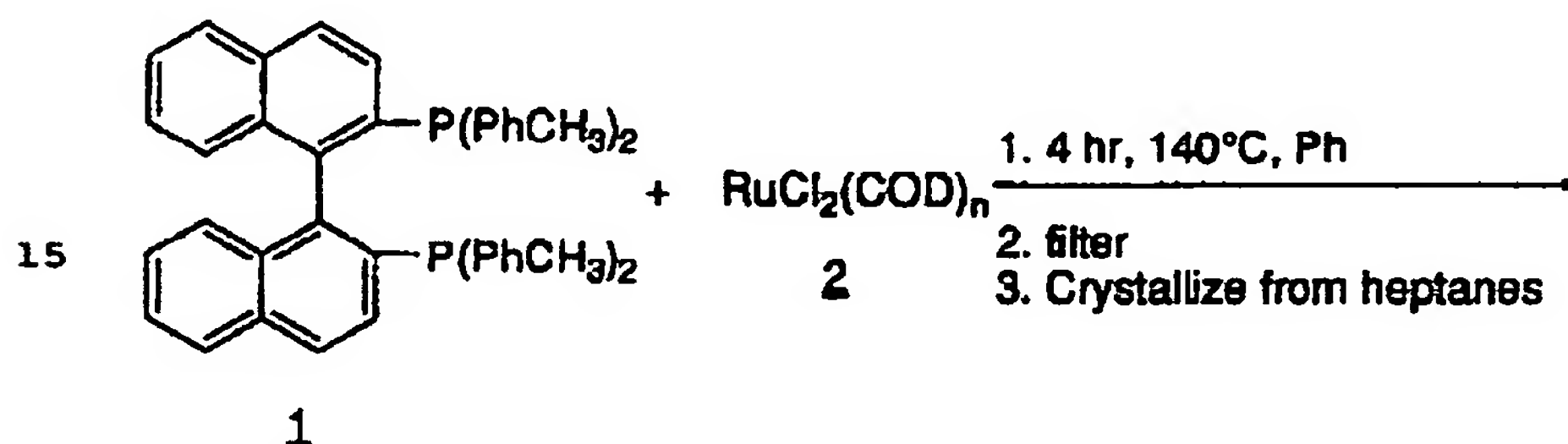
- 14 -

To the above mixture methyl acetoacetate (20  $\mu$ L) and methanol (100  $\mu$ L) were added, and the NMR signals for species 14 immediately disappeared and methyl 4-hydroxybutyrate and 13 appeared. After standing over night, the hydroxy product was isolated.

5 Examination of the (S)-Mosher ester of methyl 4-hydroxybutyrate showed the product to be >90 % enantiomeric excess.

**EXAMPLE 2**

10  $[(C_2H_5)_2NH_2]^+ [Ru_2Cl_5((R)\text{-t-BINAP})_2]^- \cdot \text{toluene}$



To a 50 mL round bottom flask was charged 500 mg of (S)-t-BINAP 1, 197 mg of  $RuCl_2[COD]_n$  polymer 2, 1.4 mL of  $Et_3N$  and 17 mL of degassed toluene. The flask was sealed and heated to 140°C for 6 hours. The dark red homogeneous solution was cooled to ambient temperature and the solution was concentrated under reduced pressure to 8 mL. Then 12 mL of heptanes was added and the solution

30

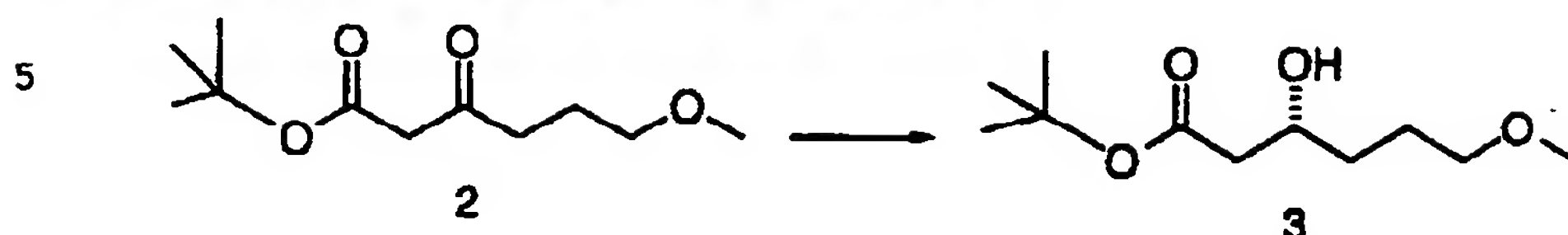
- 15 -

was stirred for one hour. The Ruthenium polymer precipitated and was filtered off via double ended filter. The homogeneous solution was concentrated under reduced pressure to 8 mL. Then 12 mL of heptanes was added and the solution was stirred for one hour. The catalyst  
5 precipitated and was filtered off via doubled ended funnel (schlenk ware). The precipitate was dried under vacuum, giving 300 mg of light yellow solid for 55% yield.

### EXAMPLE 3

10  $[(C_2H_5)_2NH_2]_2[Ru_2Cl_5((R)-BINAP)_2]$ -xylene  
(Cyclooctadienyl)ruthenium dichloride (2.14 g, 7.6 mmol) and (R)-BINAP (5.00 g, 8.0 mmol) were placed in a 50 mL round bottom flask and connected to a double ended filter (Kontes #215500-  
15 6044) with a 1000 mL round bottom flask at the opposite end. Vacuum grease was used to ensure an air-tight seal. The entire apparatus was evacuated and filled with nitrogen. Dry xylenes (170 mL) and dry triethylamine (17 mL), which had been deoxygenated with flowing nitrogen for several minutes, were added via the lower side arm. The  
20 mixture was heated to 140°C producing a deep brick red colored solution. After 4 hours the apparatus was allowed to cool to room temperature with vigorous stirring while the catalyst precipitated. The apparatus inverted to filter the product using vacuum on the lower side arm and nitrogen on the upper. The precipitate was washed with  
25 deoxygenated xylene (17 mL), and the flask containing the filtrate was exchanged for an empty one. The entire apparatus was put under vacuum and the product was dried overnight to give 440 mg (69%) of a dark red solid:  $^1H$  NMR ( $CD_2Cl_2$ , 400.13 MHz)  $\delta$  8.07 (t, J=8.8 Hz, 4H), 7.82 (t, J=8.3 Hz, 2H), 7.65 (m, J=8.3 Hz, 6H), 7.55 (m, 4H), 7.47 (m, 4H), 7.4-7.1 (om, 20H), 6.95 (m, 2H), 6.84 (t, J=7.4 Hz, 2H), 6.8-6.7 (om, 4H), 6.7-6.6 (om, 4H), 6.6-6.5 (om, 12H), 3.24 (m, 6H), 2.5-2.3 (3 singlets, 6H), 1.45 (t, J=7.3 Hz, 9H);  $^{31}P$  NMR ( $CD_2Cl_2$ , 161.98 MHz)  $\delta$  56.5 (d, J=38.0 Hz), 52.3 (d, J=38.0 Hz).  
30

- 16 -

EXAMPLE 4t-Butyl 3-hydroxy-6-methoxy hexanoate

10 Step A: Preparation of t-butyl 3-keto-6-methoxy hexanoate  
(Ketoester 2)

The dianion of methyl acetoacetate, generated with sodium hydride and n-butyl lithium in THF at -15°C, is alkylated with 1.2 equivalents of bromoethyl methyl ether. The reaction proceeds in 6-8 hours to a level of 3 wt% residual starting material and is worked up with methyl t-butyl ether (MTBE) and saturated ammonium chloride solution. Residual methyl acetoacetate (b.p. 159°C) is removed by flushing crude product with four to seven volumes of xylene to provide the alkylated ketoester containing <0.25 wt% methyl acetoacetate in 73-77% yield.

20 The methyl ester is transesterified to the t-butyl ester in 95:5-toluene:t-butanol by refluxing the solvent through 5A molecular sieves. The boiling point of the solvent mixture is 107-111°C, well above the boiling point of t-butanol, which can be slowly lost from the vessel and must be replaced as needed. After concentration, the t-butyl ester is produced in 95% yield with <1% remaining methyl ester.

25 Step B: Preparation of t-butyl 3-hydroxy-6-methoxy hexanoate (β-hydroxyester 3)

30 The hydrogenation catalyst  $[(C_2H_5)_2NH_2]^+[Ru_2Cl_5((R)-BINAP)_2]^-$  is not commercially available and must be prepared from  $[RuCl_2(COD)]_n$  and (R)-BINAP (see Example 1). Twenty gram batches are conveniently prepared in a 1L flask. Use of a double ended filter allows convenient isolation of the product on this scale. The catalyst, which can be handled and weighed in air, should be stored under nitrogen.

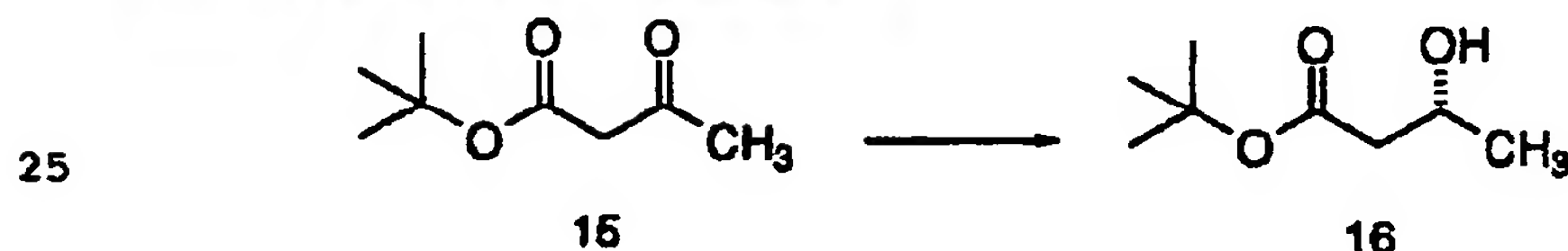
Asymmetric reduction of ketoester 2 is conducted in methanol at 45°C under 1034 N/mm<sup>2</sup> (150 psi) hydrogen with 0.09 mol% (0.4 wt%) [(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NH<sub>2</sub>]<sup>+</sup>[Ru<sub>2</sub>Cl<sub>5</sub>((R)-BINAP)<sub>2</sub>]<sup>-</sup>. The reaction mixture should be deoxygenated with nitrogen and the vessel thoroughly evacuated and flushed with nitrogen prior to pressurization with hydrogen. The reaction is exothermic and requires periodic cooling to maintain the temperature at 45°. After 4 hours hydrogen uptake is complete and the catalyst is precipitated with hexane and filtered away. Concentration provides a >97% yield of the alcohol whose enantiomeric excess is determined to be 97% by proton NMR analysis of the derived Mosher ester.

The hydrogenation reaction is very susceptible to the presence of basic impurities and acidification of these with small amounts of strong acid is required.

15                      Transesterification during the reaction can result from either high temperatures or the presence of excess amounts of acid. Thus, the reaction temperature should be kept at 45° and the minimum possible amount of HCl should be used.

20 **EXAMPLE 5**

**tert-Butyl 3(R)-hydroxybutyrate**



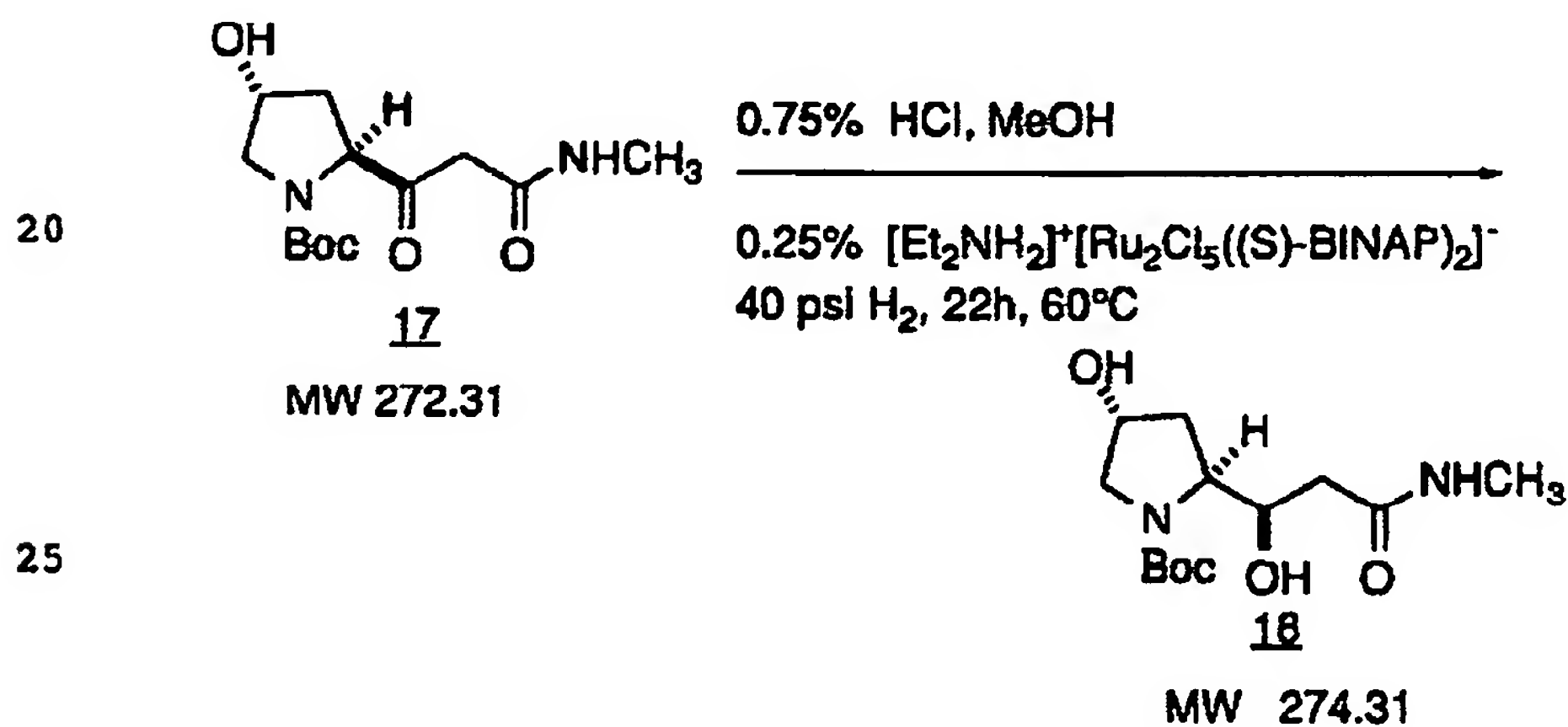
30 tert-Butyl acetoacetate [15] (14.5 g, 90 mmol) and methanol (30 mL) were mixed and deoxygenated with flowing nitrogen for 5 minutes in a septum covered Parr shaker bottle. The catalyst prepared as described above (36 mg, 0.02 mmol) was added along with 2N HCl (0.041 mL, 0.082 mmol). The mixture was transferred to a standard Parr shaker apparatus and flushed by evacuating and refilling with nitrogen and then hydrogen several times. The apparatus was heated at 40°C with shaking under 50 psi of hydrogen. After 20 min the reaction

- 18 -

became a homogeneous clear yellow solution which took up hydrogen for approximately eight hours. At this time the reaction was complete and the mixture was cooled and diluted with hexane (30 mL) to precipitate the catalyst, which was filtered away. The filtrate was concentrated to give tert-butyl 3(R)-hydroxybutyrate [16] (14.5 g, 97%).

**EXAMPLE 6****tert-Butyl 3(R)-hydroxybutyrate**

Following the procedure described in Example 3 with the exception that 2N H<sub>2</sub>SO<sub>4</sub> was substituted for the 2N HCl tert-butyl acetoacetate was reduced to the titled product.

**EXAMPLE 7**

In a 25 mL round bottom flask with a septum the  $\beta$ -keto amide **17** (1 g) was dissolved in methanol (4 mL). The solution was deoxygenated with nitrogen for 20 minutes and then the finely ground  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{S})\text{-BINAP})_2]^-$  catalyst (15.5 mg) (prepared as described in Example 1) was added. The solution was degassed with nitrogen for 5 minutes and 2N hydrochloric acid (0.092 mL) was

- 19 -

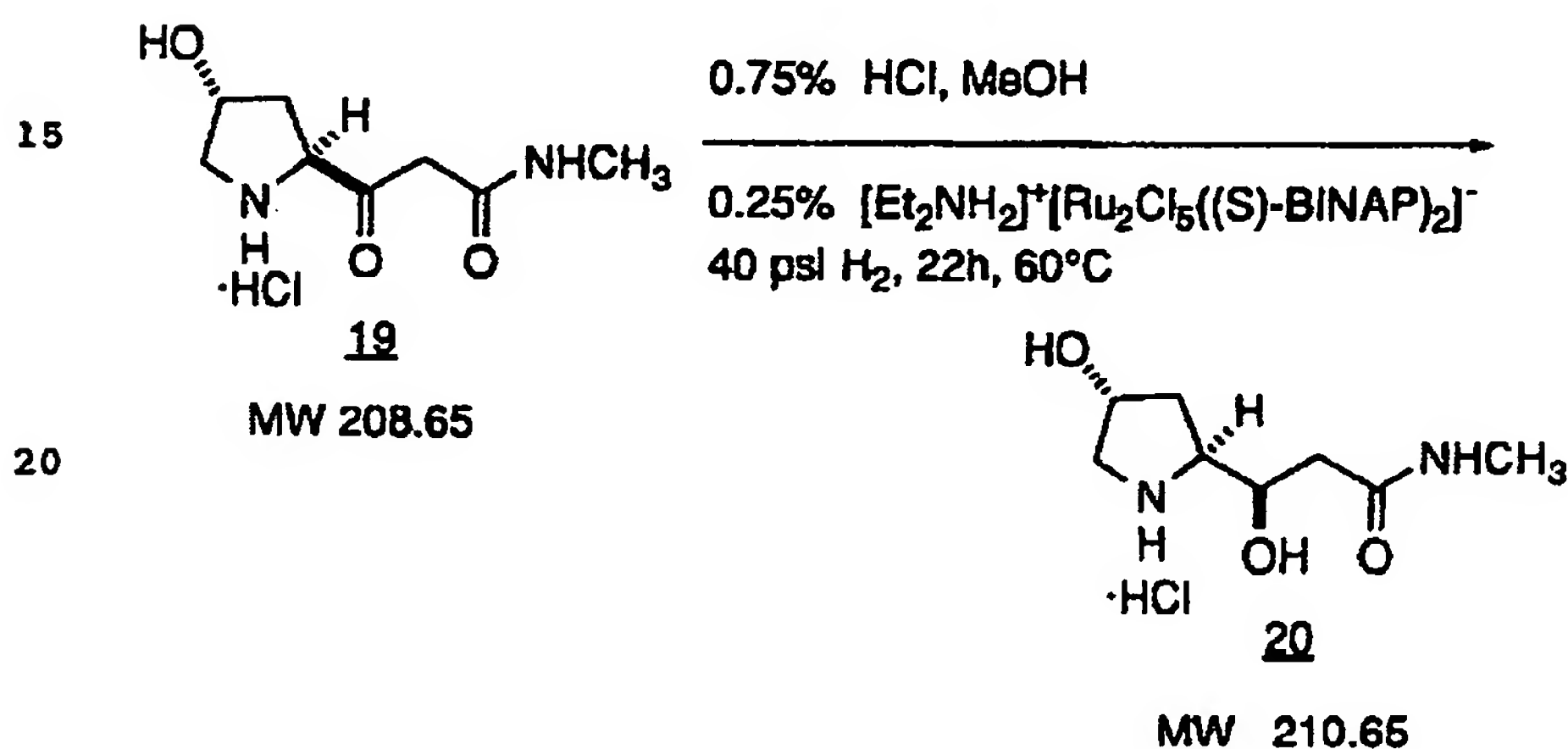
added. The mixture was cannulated into the reaction pressure vessel. The apparatus was heated at 60°C with shaking under 40 psi of hydrogen for 20 hours.

After 20 h the reaction mixture was removed from the reaction pressure vessel. The vessel was rinsed with methanol (3 mL) which was combined with the reaction mixture. The solution was concentrated under reduced pressure to an off-white solid.

The crude reaction mixture gave a 87:13 ratio of the R:S hydroxy esters.

The yield was 100%.

### EXAMPLE 8



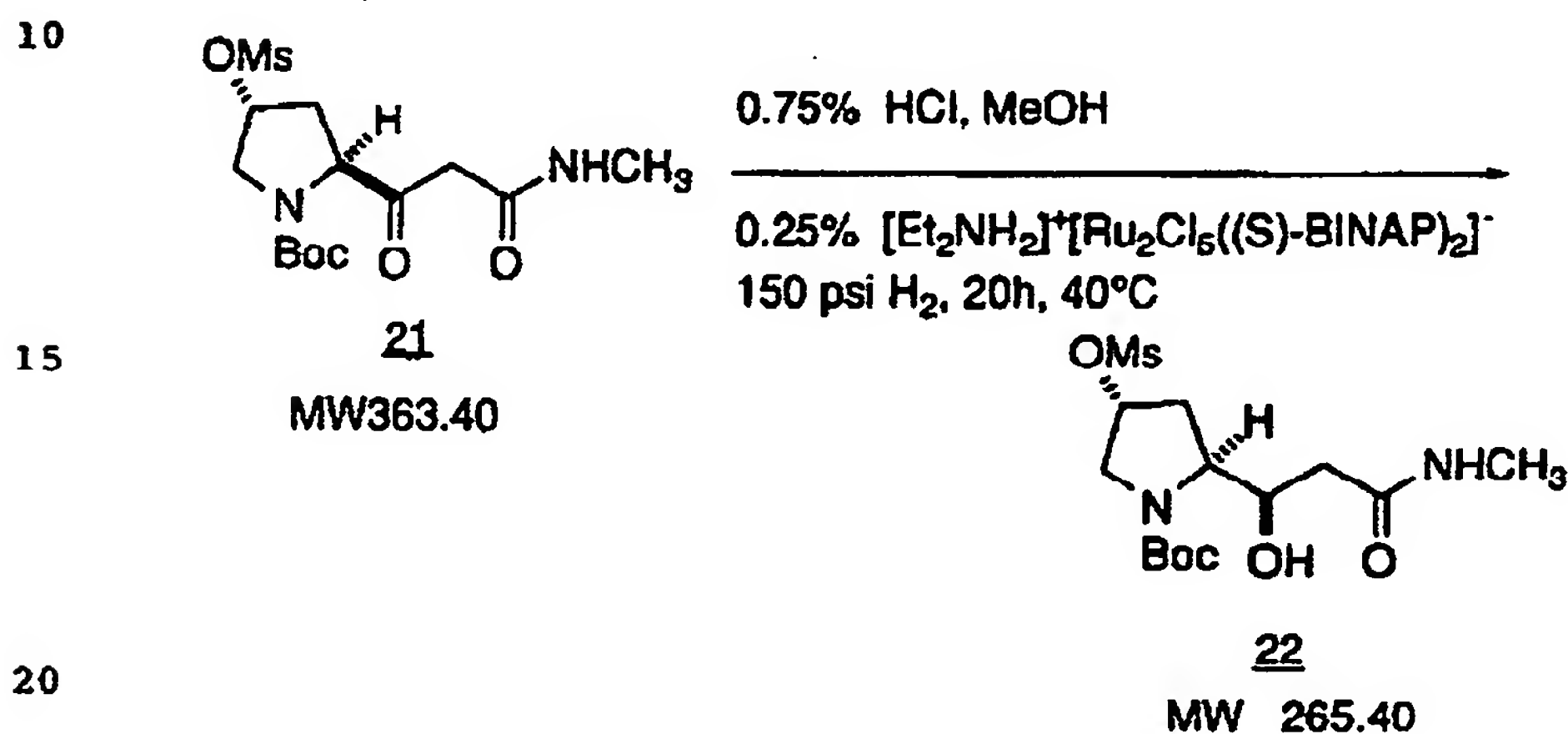
In a 25 mL round bottom flask with a septum the  $\beta$ -keto amide HCL salt 19 (1 g) was dissolved in methanol (16 mL). The solution was deoxygenated with nitrogen for 20 minutes and then the finely ground  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{S})\text{-BINAP})_2]^-$  catalyst (20.2 mg) (prepared as described in Example 1) was added. The solution was degassed with nitrogen for 5 minutes and 2N hydrochloric acid (0.120 mL) was added. The mixture was cannulated into the reaction pressure vessel. The apparatus was heated at 60°C with shaking under 40 psi of hydrogen for 20 hours.

- 20 -

After 20 h the reaction mixture was removed from the reaction pressure vessel. The vessel was rinsed with methanol (3 mL) which was combined with the reaction mixture. The solution was concentrated under reduced pressure to an off-white solid. The crude reaction mixture gave a 97:3 ratio of the R:S hydroxy amides.

The yield was 80%.

### EXAMPLE 9



In a 25 mL round bottom flask with a septum the  $\beta$ -keto amide mesylate **21** (0.957 g) was dissolved in methanol (2.5 mL). The solution was deoxygenated with nitrogen for 20 minutes and then the finely ground  $[(\text{C}_2\text{H}_5)_2\text{NH}_2]^+[\text{Ru}_2\text{Cl}_5((\text{S})\text{-BINAP})_2]^-$  catalyst (11 mg) (prepared as described in Example 1) was added. The solution was degassed with nitrogen for 5 minutes and 2N hydrochloric acid (0.020 mL) was added. The mixture was cannulated into the reaction pressure vessel. The apparatus was heated at 40°C with stirring under 150 psi of hydrogen for 20 hours.

After 20 h the reaction mixture was removed from the reaction pressure vessel. The vessel was rinsed with methanol (3 mL) which was combined with the reaction mixture. The solution was



- 21 -

concentrated under reduced pressure to an off-white solid. The crude reaction mixture gave a 91:9 ratio of the R:S hydroxy amide mesylates. The yield was 80%.

5

#### EXAMPLE 10

##### (R)-Trans-2-Methoxycarbonylcyclopentanol

2-Methoxycarbonyl-cyclopentanone (4.26 g) was dissolved in methanol (5 mL) and 0.1 mL 1N HCl was added. The mixture was deoxygenated, 1 (36 mg) was added and the mixture was exposed to hydrogen at 40 psi and 40° in a Parr shaker apparatus. After 6 h the reaction was complete, providing a single product (4.10 g) in >95% ee: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) 4.40 (q, J=7.5 Hz, 1H), 3.71 (s, 3H), 2.65 (q, J=7.2 Hz, 1H), 2.1-1.5 (m, 6H).

15

#### EXAMPLE 11

##### Methyl 3-Hydroxy-2-methylbutyrate

Methyl 2-methylacetoacetate was hydrogenated under the conditions set forth in Example 2 or 3, to give a 6:4 mixture of trans:cis product. Enantiomeric excess of the major isomer was >97%.

20

#### EXAMPLE 12

##### Methyl 5-(R)-hydroxyvalerate

A mixture of methyl levulinate (10.0 g, 77 mmol), methanol (10 mL) and concentrated HCl (0.4 mL) was deoxygenated with bubbling nitrogen for 2 minutes. [(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NH<sub>2</sub>]<sup>+</sup>[Ru<sub>2</sub>Cl<sub>5</sub>((R)-BINAP)<sub>2</sub>]<sup>-</sup> (50 mg) was added and the mixture placed in a standard Parr shaker apparatus. After evacuating and flushing with nitrogen three times, the mixture was evacuated and exposed to 40 psi hydrogen pressure at 40°C for 48 h. The solvent was removed in vacuo to give the product (9.90g, 99% yield) which was identical to a commercially available (Aldrich) racemic sample by <sup>1</sup>H NMR. The optical purity was shown to be 99:1 by obtaining proton NMR spectrum of the product (1

30

- 22 -

mL) and (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (27 mg) in CDCl<sub>3</sub>. Peak assignments were made by spiking with a sample of the racemate. Methyl 5-(*R*)-hydroxyvalerate spontaneously lactonizes to give 5-(*R*)- $\gamma$ -valerolactone.

5

### EXAMPLE 13

#### Ethyl 3-hydroxybutyrate

This was prepared from ethyl acetoacetate in ethanol according to the procedure of Example 4 or 5. Enantiomeric excess was measured to be 97%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) 4.20 (m, 1H), 4.10 (q, J=7.5 Hz, 1H), 2.51 (m, 2H), 1.2 (m, 5H).

15

20

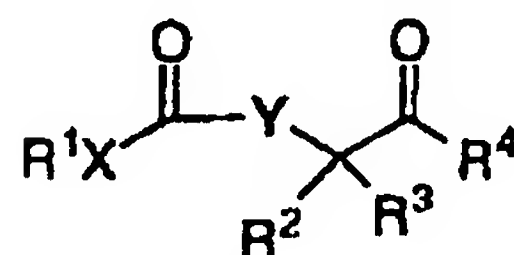
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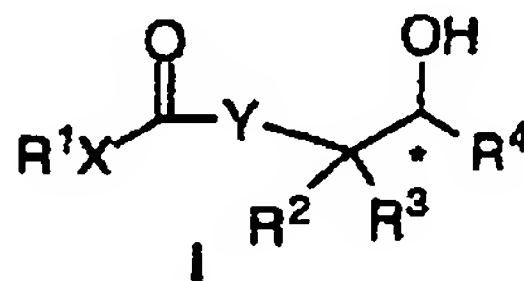
- 23 -

WHAT IS CLAIMED IS:

1. A process for the asymmetric reduction of a  $\beta$  or  $\gamma$ -ketoester or  $\beta$  or  $\gamma$ -ketoamide of structural formula:



to form a  $\beta$  or  $\gamma$ -hydroxyester or  $\beta$  or  $\gamma$ -hydroxyamide of formula I:



wherein:

R<sup>1</sup> is straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

X is O or NR<sup>5</sup>;

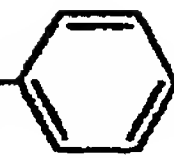
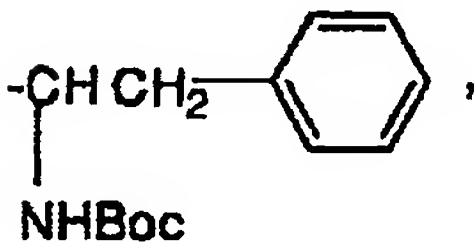
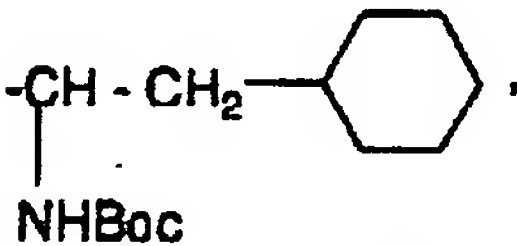
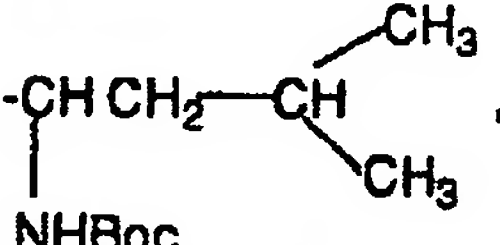
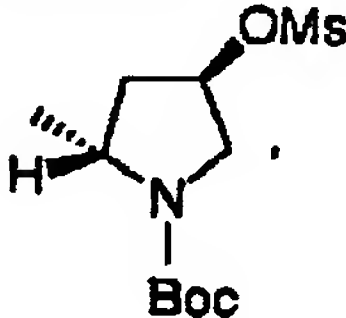
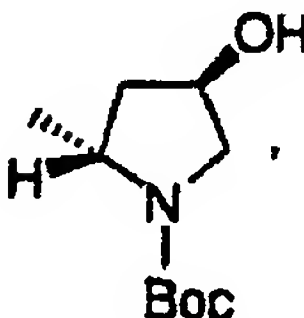
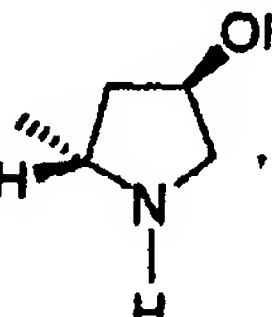

Y is C(R<sup>2</sup>)<sub>2</sub> or a single bond;

R<sup>2</sup> is: H, or straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>3</sup> is: H, straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl, CH<sub>2</sub>NHCOR<sup>6</sup>, or R<sup>1</sup> and R<sup>3</sup> taken together form a lactone or cyclic amide of 5 to 7 atoms one of which is an oxygen or nitrogen;

- 24 -

R<sup>4</sup> is :

- (a) CH<sub>3</sub>,
- (b) CH<sub>2</sub>Cl,
- 5 (c) CH<sub>2</sub>OCH<sub>2</sub>--OCH<sub>3</sub>,
- (d) ,
- 10 (e) ,
- (f) ,
- 15 (g) ,
- 20 (h) ,
- 25 (i) ,
- 30 (j) -CH<sub>2</sub>--CH<sub>3</sub>, or
- (k) CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>;

- 25 -

$R^3$  and  $R^4$  taken together form a ring of 5 to 7 carbons, in which  
 $R^3$  and  $R^4$  represent a carbon chain of 3 to 5 carbons;

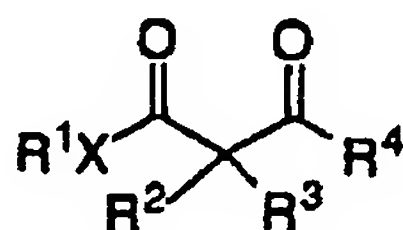
5  $R^5$  is H, straight or branched  $C_1$ - $C_4$  alkyl, or  $CO_2$   $C_1$ - $C_4$  alkyl;  
 and

$R^6$  is straight or branched  $C_1$ - $C_4$  alkyl, or O- $C_1$ - $C_4$  alkyl,  
 10 phenyl, O-benzyl;

which comprises treating the  $\beta$ - or  $\gamma$ -ketoester or  $\beta$ - or  $\gamma$ -ketoamide in  
 a  $C_1$ - $C_3$  alkanol with a Ru(II)-BINAP derived catalyst in the presence  
 of a strong acid at about 40-50°C and about 50 to 1400 N/mm<sup>2</sup> of  
 15 hydrogen.

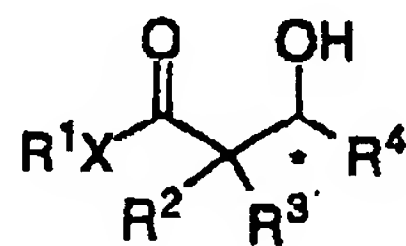
2. The process of Claim 1 for the asymmetric reduction  
 of a  $\beta$ -ketoester or  $\beta$ -ketoamide of structural formula:

20



to form the  $\beta$ -hydroxyester or  $\beta$ -hydroxyamide of formula:

25



30 wherein:

$R^1$  is straight or branched  $C_1$ - $C_4$  alkyl;

X is O or  $NR^5$ ;

- 26 -


R<sup>2</sup> is: H, or straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;

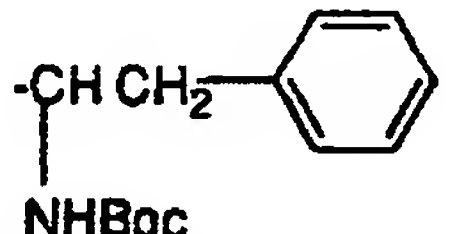
R<sup>3</sup> is: H, straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl, CH<sub>2</sub>NHCOR<sup>6</sup>, or R<sup>1</sup>  
and R<sup>3</sup> taken together form a lactone or cyclic amide of 5  
to 7 atoms one of which is an oxygen or nitrogen;

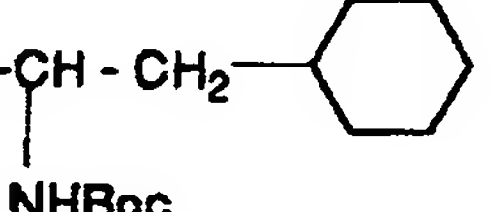
R<sup>4</sup> is :

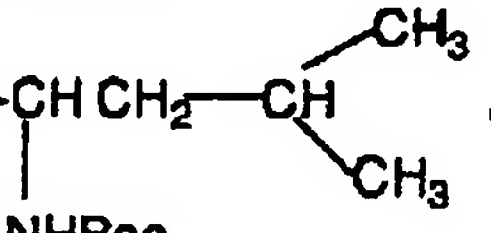
(a) CH<sub>3</sub>,

(b) CH<sub>2</sub>Cl,

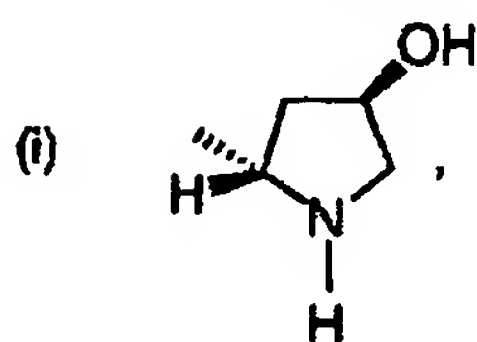
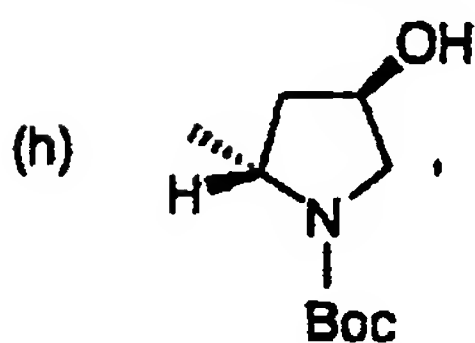
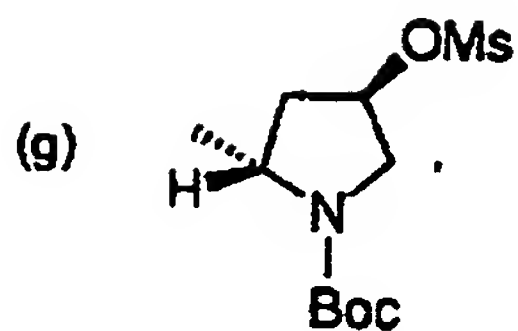
(c) CH<sub>2</sub>OCH<sub>2</sub>--OCH<sub>3</sub>,

(d) ,

(e) ,

(f) .

- 27 -



R<sup>3</sup> and R<sup>4</sup> taken together form a ring of 5 to 7 carbons, in which  
R<sup>3</sup> and R<sup>4</sup> represent a carbon chain of 3 to 5 carbons;

R<sup>5</sup> is H, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or CO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl;  
and

R<sup>6</sup> is straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or O-C<sub>1</sub>-C<sub>4</sub> alkyl,  
phenyl, O-benzyl;

which comprises treating the  $\beta$ -ketoester in a C<sub>1</sub>-C<sub>3</sub> alkanol with a  
Ru(II)-BINAP derived catalyst in the presence of a strong acid at about  
40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen.



- 28 -

3. The process of Claim 1 wherein the Ru(II)-BINAP derived catalyst is  $[(C_2H_5)_2NH_2]^+[Ru_2Cl_5(BINAP)_2]^- \cdot \text{solvate}$ .

5 4. The process of Claim 3 wherein the solvate is selected from the group consisting of benzene, toluene, xylene, chlorobenzene, or 1,2-, 1,3-, or 1,4-dichlorobenzene.

10 5. The process of Claim 4 wherein C<sub>1-3</sub> alkanol is methanol.

6. The process of Claim 5 wherein the concentration of the  $\beta$ -ketoester in the reaction mixture is about 0.5 to 2.25 molar.

15 7. The process of Claim 6 wherein the amount of catalyst is about 0.02 to 0.1 mole%.

8. The process of Claim 7 wherein the strong acid is selected from the group consisting of HCl, H<sub>2</sub>SO<sub>4</sub>, or CH<sub>3</sub>SO<sub>4</sub>.

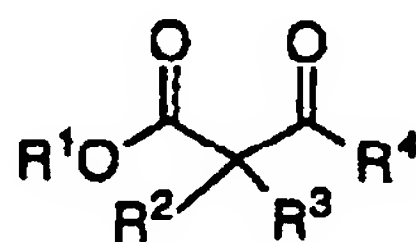
20 9. The process of Claim 8 wherein the concentration of the strong acid is about 0.1 to 10 mole %.

25 10. The process of Claim 9, wherein the strong acid is HCl.

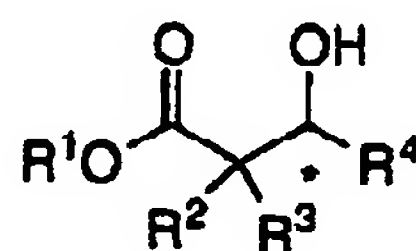
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- 29 -

11. The process of Claim 9 wherein the asymmetric reduction of a  $\beta$ -ketoester of structural formula:



to form the  $\beta$ -hydroxyester of formula:



15 wherein:

$\text{R}^1$  is straight or branched  $\text{C}_1$ - $\text{C}_4$  alkyl;


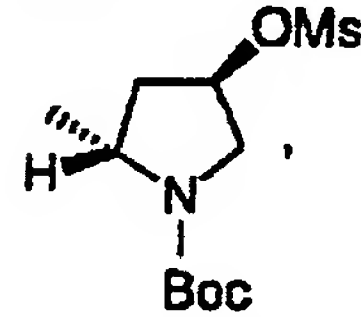
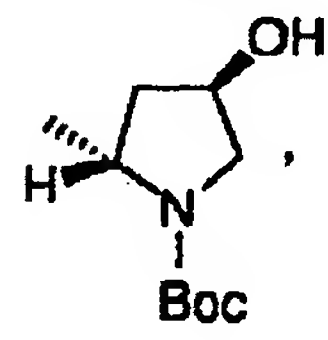
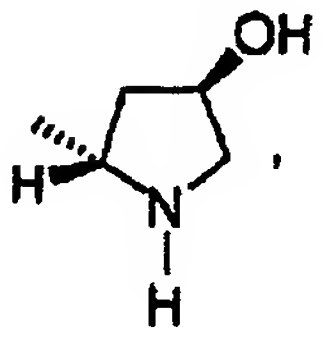
$\text{R}^2$  and  $\text{R}^3$  are: H;

$\text{R}^4$  is :

25

30

- 30 -

- 5
- (a)  $\text{CH}_3$ ,
- (b)  $\text{CH}_2\text{Cl}$ ,
- (c)  $\text{CH}_2\text{OCH}_2$ -- $\text{OCH}_3$ ,
- 10
- (d)  $\text{-CH(CH}_2\text{-C}_6\text{H}_5\text{)NH-Boc}$ ,
- (e)  $\text{-CH(CH}_2\text{-C}_6\text{H}_{11}\text{)NH-Boc}$ ,
- 15
- (f)  $\text{-CH(CH}_2\text{-CH(CH}_3\text{)}_2\text{)NH-Boc}$ ,
- (g) ,
- 20
- (h) ,
- 25
- (i) ,
- 30
- (j)  $\text{-CH}_2\text{-CH=CH-CH}_3$ , or
- (k)  $\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$ ;

- 31 -

R<sup>3</sup> and R<sup>4</sup> taken together form a ring of 5 to 7 carbons, in which  
R<sup>3</sup> and R<sup>4</sup> represent a carbon chain of 3 to 5 carbons; and

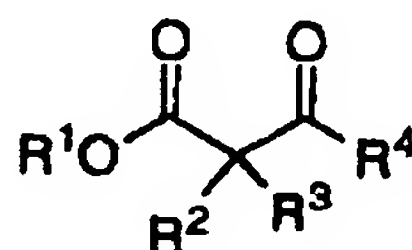
5 R<sup>5</sup> is H, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or CO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl;

which comprises treating the  $\beta$ -ketoester in a C<sub>1</sub>-C<sub>3</sub> alkanol with a  
Ru(II)-BINAP derived catalyst in the presence of a strong acid at about  
40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen.

10

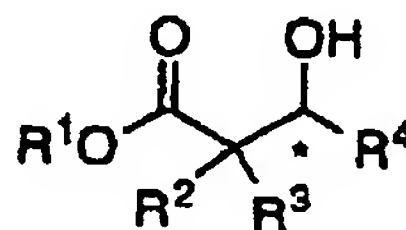
12. The process of Claim 10 for the asymmetric  
reduction of a  $\beta$ -ketoester of structural formula:

15



to form the  $\beta$ -hydroxyester of formula:

20



25 wherein:

R<sup>1</sup> is methyl, ethyl or t-butyl; and

R<sup>2</sup> and R<sup>3</sup> are; H;

30

R<sup>4</sup> is CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, or R<sup>3</sup> and R<sup>4</sup> taken  
together form a ring of 5 carbons, in which R<sup>3</sup> and R<sup>4</sup>  
represent a carbon chain of 3 carbons;

- 32 -

which comprises treating the  $\beta$ -ketoester in a C<sub>1</sub>-C<sub>3</sub> alkanol with a Ru(II)-BINAP derived catalyst in the presence of a strong acid at about 40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen.

- 5                    13. The process of Claim 9 wherein the asymmetric reduction of a  $\beta$ -ketoamide of structural formula:



to form the  $\beta$ -hydroxyamide of formula:



wherein:

20

$R^1$  is straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;


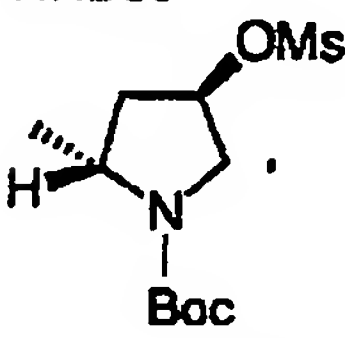
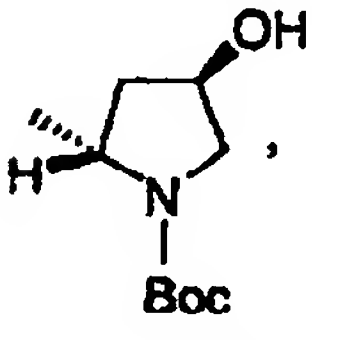
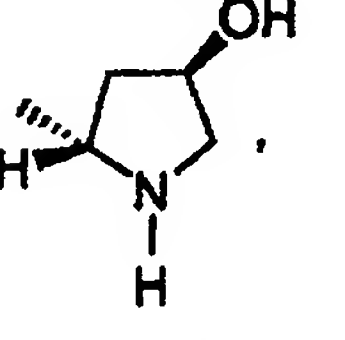

$R^2$  and  $R^3$  are: H;

25

$R^4$  is :

30

- 33 -

- 5
- (a)  $\text{CH}_3$ ,
- (b)  $\text{CH}_2\text{Cl}$ ,
- (c)  $\text{CH}_2\text{OCH}_2$ -- $\text{OCH}_3$ ,
- 10
- (d)  $\begin{array}{c} \text{CH} \text{CH}_2 \text{---} \text{C}_6\text{H}_5 \\ | \\ \text{NHBoc} \end{array}$ ,
- (e)  $\begin{array}{c} \text{CH} \text{---} \text{CH}_2 \text{---} \text{C}_6\text{H}_{11} \\ | \\ \text{NHBoc} \end{array}$ ,
- 15
- (f)  $\begin{array}{c} \text{CH} \text{CH}_2 \text{---} \text{CH} \begin{array}{l} \text{CH}_3 \\ \text{CH}_3 \end{array} \\ | \\ \text{NHBoc} \end{array}$ ,
- (g) ,
- 20
- (h) ,
- 25
- (i) ,
- 30
- (j)  $-\text{CH}_2$ -- $\text{CH}_3$ , or
- (k)  $\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$ ;

- 34 -

$R^3$  and  $R^4$  taken together form a ring of 5 to 7 carbons, in which  
 $R^3$  and  $R^4$  represent a carbon chain of 3 to 5 carbons; and

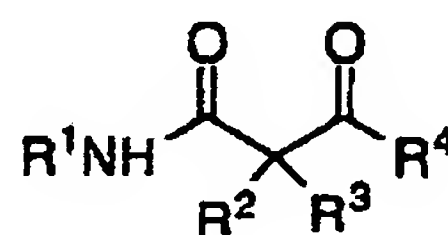
5  $R^5$  is H, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or CO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl;

which comprises treating the  $\beta$ -ketoamide in a C<sub>1</sub>-C<sub>3</sub> alkanol with a  
 Ru(II)-BINAP derived catalyst in the presence of a strong acid at about  
 40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen.

10

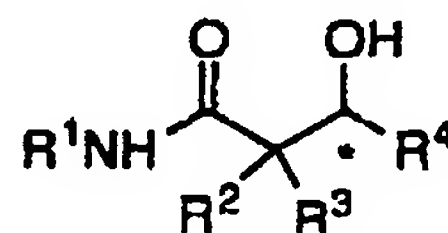
14. The process of Claim 10 for the asymmetric  
 reduction of a  $\beta$ -ketoamide of structural formula:

15



to form the  $\beta$ -hydroxyamide of formula:

20



25

wherein:

$R^1$  is methyl, ethyl or t-butyl; and

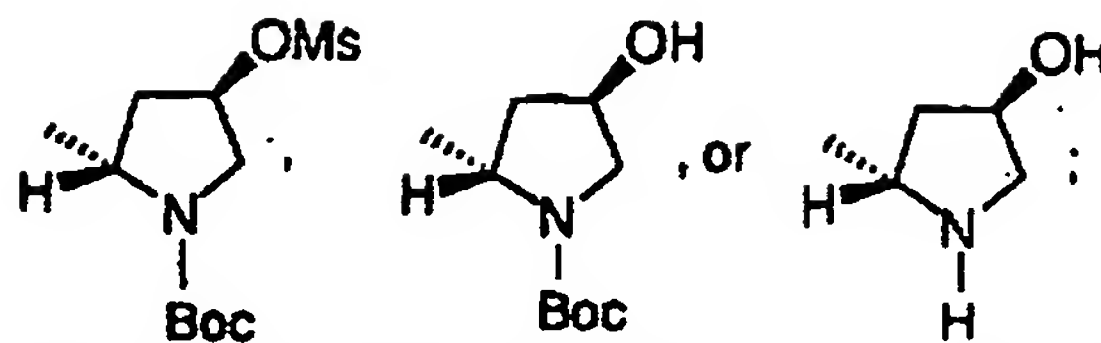
$R^2$  and  $R^3$  are: H;

30

$R^4$  is :

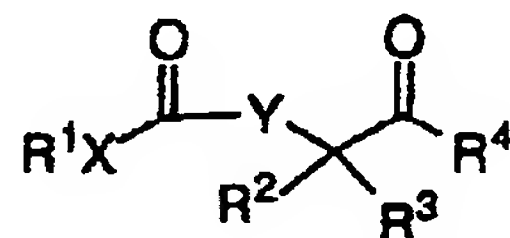


- 35 -



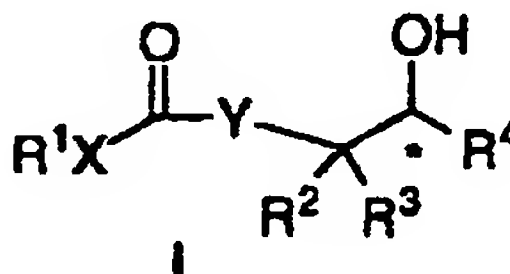
5 which comprises treating the  $\beta$ -ketoamide in a C<sub>1</sub>-C<sub>3</sub> alkanol with a Ru(II)-BINAP derived catalyst in the presence of a strong acid at about 40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen.

10 15. In a process for the asymmetric reduction of a  $\beta$  or  $\gamma$ -ketoester or  $\beta$  or  $\gamma$ -ketoamide of structural formula:



15

to form a  $\beta$  or  $\gamma$ -hydroxyester or  $\beta$  or  $\gamma$ -hydroxyamide of formula I:



20

in the presence of a Ru(II)-BINAP derived catalyst at elevated temperature and pressure, wherein:

25 R<sub>1</sub> is straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

X is O or NR<sup>5</sup>;

30 Y is C(R<sup>2</sup>)<sub>2</sub> or a single bond;

R<sub>2</sub> is: H, or straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl;


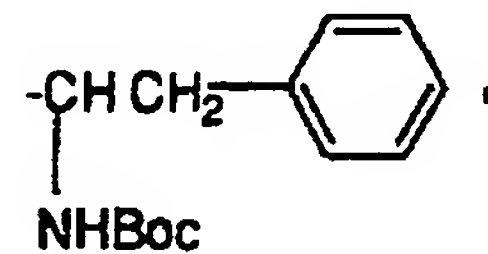
- 36 -

$R^3$  is: H, straight or branched  $C_1$ - $C_6$  alkyl,  $CH_2NHCOR^6$ , or  $R^1$  and  $R^3$  taken together form a lactone or cyclic amide of 5 to 7 atoms one of which is an oxygen or nitrogen;

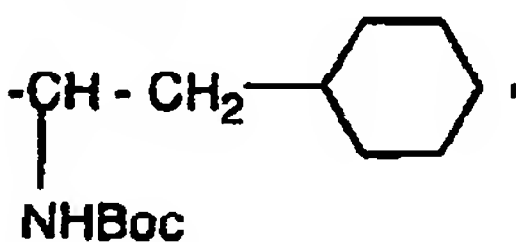
5

 $R^4$  is :(a)  $CH_3$ ,(b)  $CH_2Cl$ ,

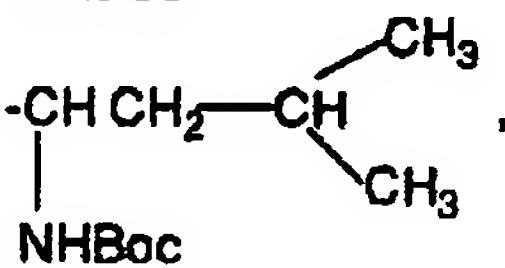
10

(c)  $CH_2OCH_2$ -- $OCH_3$ ,(d) ,

15

(e) ,

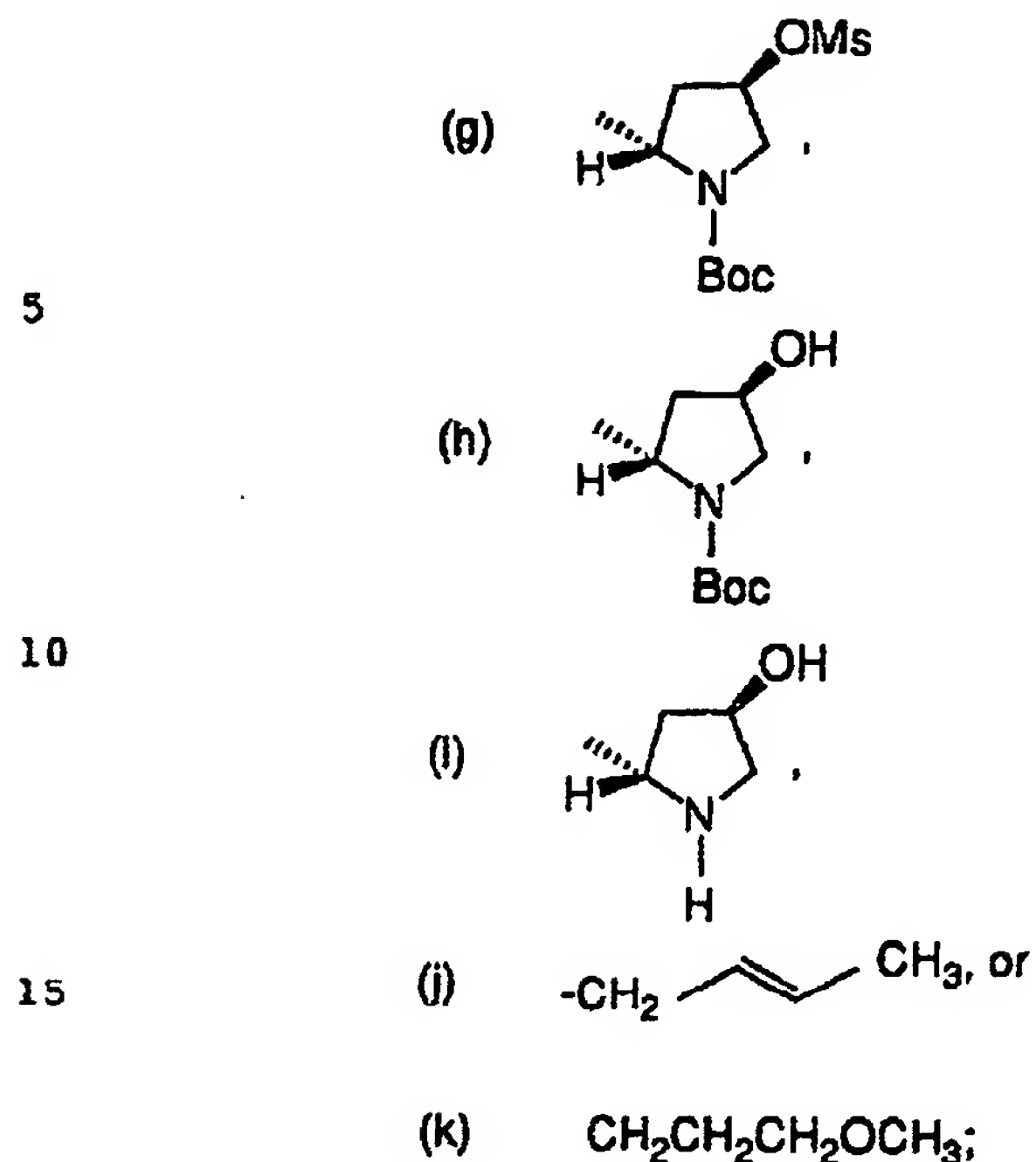
20

(f) ,

25

30

- 37 -



20  $\text{R}^3$  and  $\text{R}^4$  taken together form a ring of 5 to 7 carbons, in which  
 $\text{R}^3$  and  $\text{R}^4$  represent a carbon chain of 3 to 5 carbons;

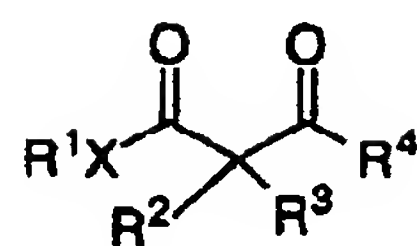
$\text{R}^5$  is H, straight or branched  $\text{C}_1$ - $\text{C}_4$  alkyl, or  $\text{CO}_2$   $\text{C}_1$ - $\text{C}_4$  alkyl;  
 and

25  $\text{R}^6$  is straight or branched  $\text{C}_1$ - $\text{C}_4$  alkyl, or O- $\text{C}_1$ - $\text{C}_4$  alkyl,  
 phenyl, O-benzyl;

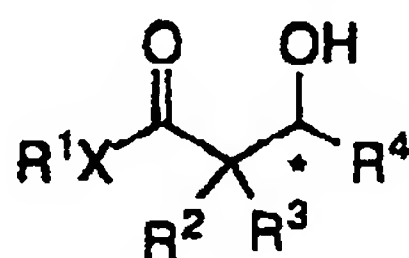
30 and the improvement comprises conducting the reduction at about 40-  
 50°C and about 50 to 1400  $\text{N/mm}^2$  of hydrogen, in the presence of a  
 strong acid.

16. In a process for the asymmetric reduction of a  
 $\beta$  or  $\gamma$ -ketoester or  $\beta$  or  $\gamma$ -ketoamide of structural formula:

- 38 -



5 to form the  $\beta$ -hydroxyester or  $\beta$ -hydroxyamide of formula:



10

in the presence of a Ru(II)-BINAP derived catalyst at elevated temperature and pressure, wherein:

15  $\text{R}^1$  is straight or branched  $\text{C}_1$ - $\text{C}_4$  alkyl;

$\text{X}$  is  $\text{O}$  or  $\text{NR}^5$ ;


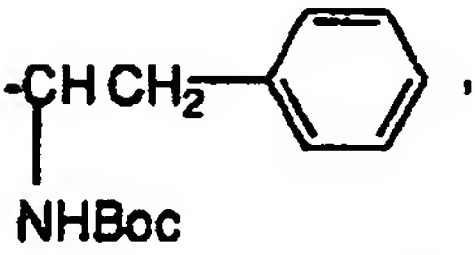
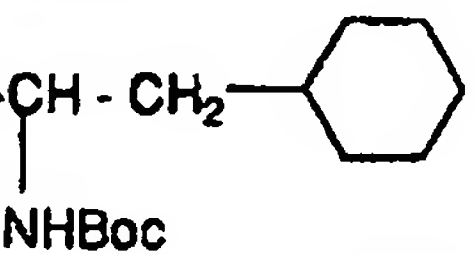
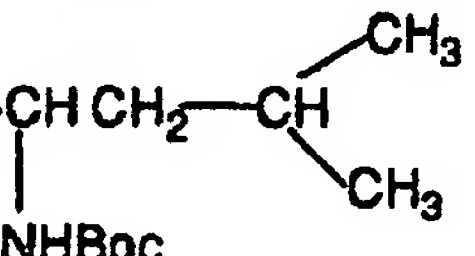
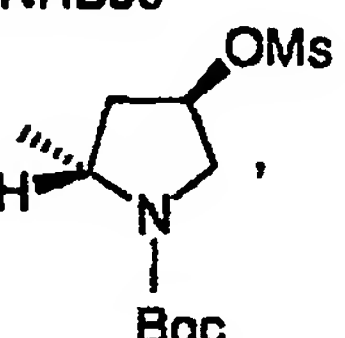
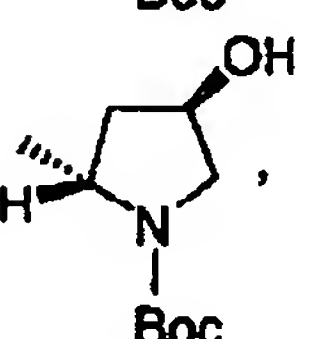
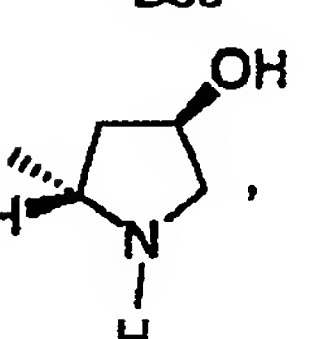
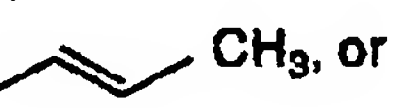
$\text{R}^2$  is:  $\text{H}$ , or straight or branched  $\text{C}_1$ - $\text{C}_6$  alkyl;

20  $\text{R}^3$  is:  $\text{H}$ , straight or branched  $\text{C}_1$ - $\text{C}_6$  alkyl,  $\text{CH}_2\text{NHCOR}^6$ , or  $\text{R}^1$  and  $\text{R}^3$  taken together form a lactone or cyclic amide of 5 to 7 atoms one of which is an oxygen or nitrogen;

25  $\text{R}^4$  is:

30

- 39 -

- 5
- (a)  $\text{CH}_3$ ,
- (b)  $\text{CH}_2\text{Cl}$ ,
- (c)  $\text{CH}_2\text{OCH}_2$ -- $\text{OCH}_3$ ,
- 10
- (d) ,
- (e) ,
- 15
- (f) ,
- (g) ,
- 20
- (h) ,
- 25
- (i) ,
- 30
- (j)  $-\text{CH}_2$ -- $\text{CH}_3$ , or
- (k)  $\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$ ;

- 40 -

R<sup>3</sup> and R<sup>4</sup> taken together form a ring of 5 to 7 carbons, in which  
R<sup>3</sup> and R<sup>4</sup> represent a carbon chain of 3 to 5 carbons;

5 R<sup>5</sup> is H, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or CO<sub>2</sub> C<sub>1</sub>-C<sub>4</sub> alkyl;  
and

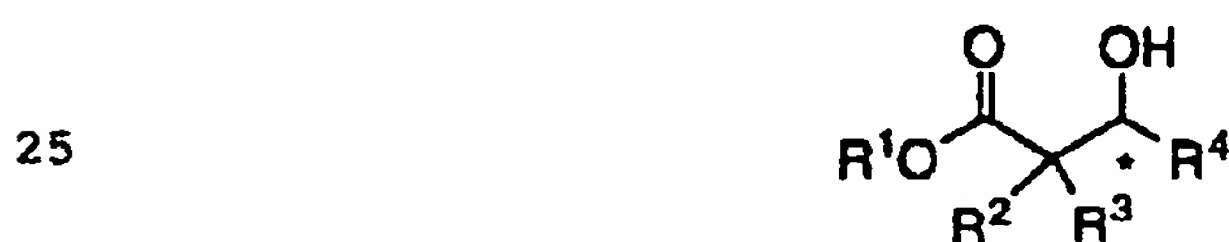
R<sup>6</sup> is straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl, or O-C<sub>1</sub>-C<sub>4</sub> alkyl,  
10 phenyl, O-benzyl;

and the improvement comprises conducting the reduction at about 40-  
50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen, in the presence of a  
strong acid.

15 17. In a process for the asymmetric reduction a β-  
ketoester of structural formula:



to form the β-hydroxyester of formula:



30 in the presence of a Ru(II)-BINAP derived catalyst at elevated  
temperature and pressure, wherein:

R<sup>1</sup> is methyl, ethyl or t-butyl; and

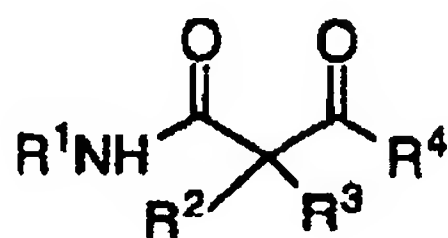
R<sup>2</sup> and R<sup>3</sup> are: H;

- 41 -

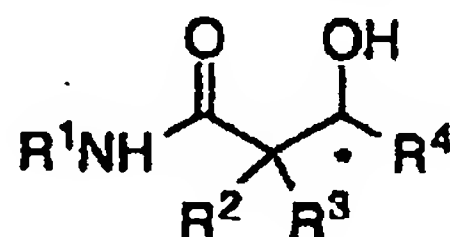
$R^4$  is  $CH_3$ ,  $CH_2CH_2CH_3$ ,  $CH_2CH_2CH_2OCH_3$ , or  $R^3$  and  $R^4$  taken together form a ring of 5 carbons, in which  $R^3$  and  $R^4$  represent a carbon chain of 3 carbons;

5 and the improvement comprises conducting the reduction at about 40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen, in the presence of a strong acid.

10 18. In a process for the asymmetric reduction of a  $\beta$ -ketoamide of structural formula:



to form the  $\beta$ -hydroxyamide of formula:

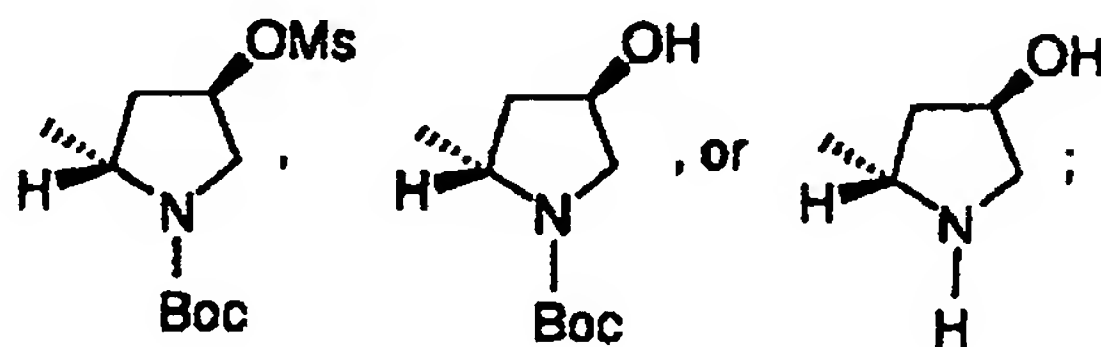


in the presence of a Ru(II)-BINAP derived catalyst at elevated temperature and pressure, wherein:

25  $R^1$  is methyl, ethyl or t-butyl; and

$R^2$  and  $R^3$  are: H;

30  $R^4$  is:

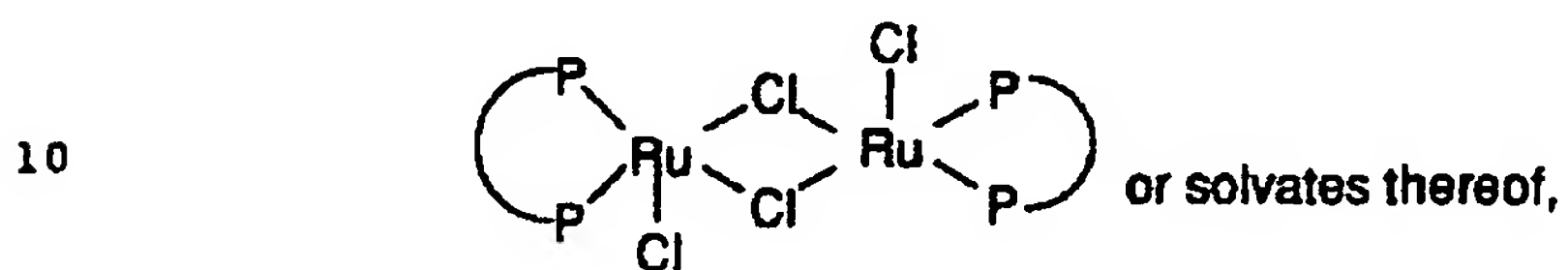


- 42 -

and the improvement comprises conducting the reduction at about 40-50°C and about 50 to 1400 N/mm<sup>2</sup> of hydrogen, in the presence of a strong acid.

5

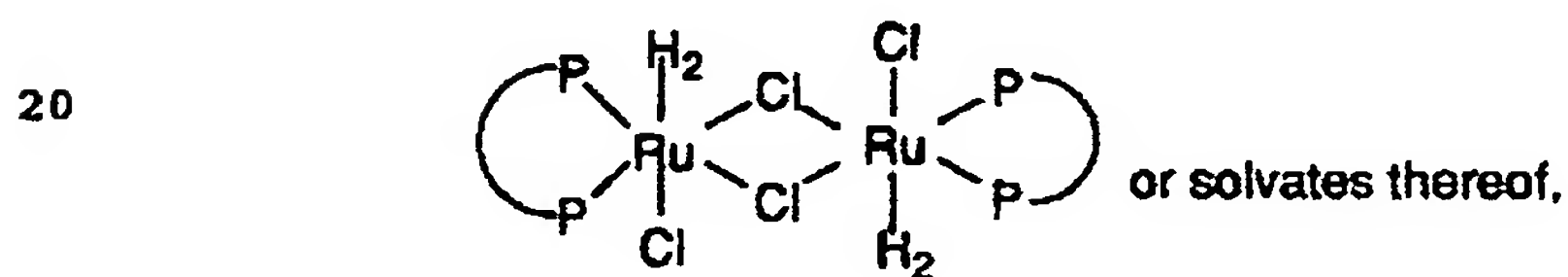
19. A compound of structural formula:



wherein:  P P represents BINAP or t-BINAP.

15

20. A compound of structural formula:



wherein:  P P represents BINAP or t-BINAP.

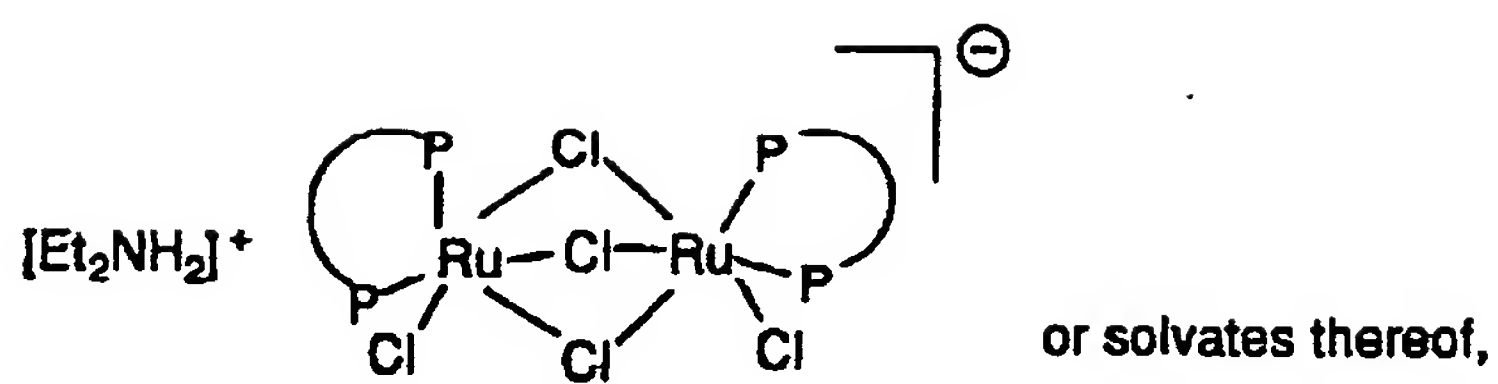
25

21. A compound of structural formula:

30



- 43 -



wherein:  P P represents BINAP or t-BINAP.

10

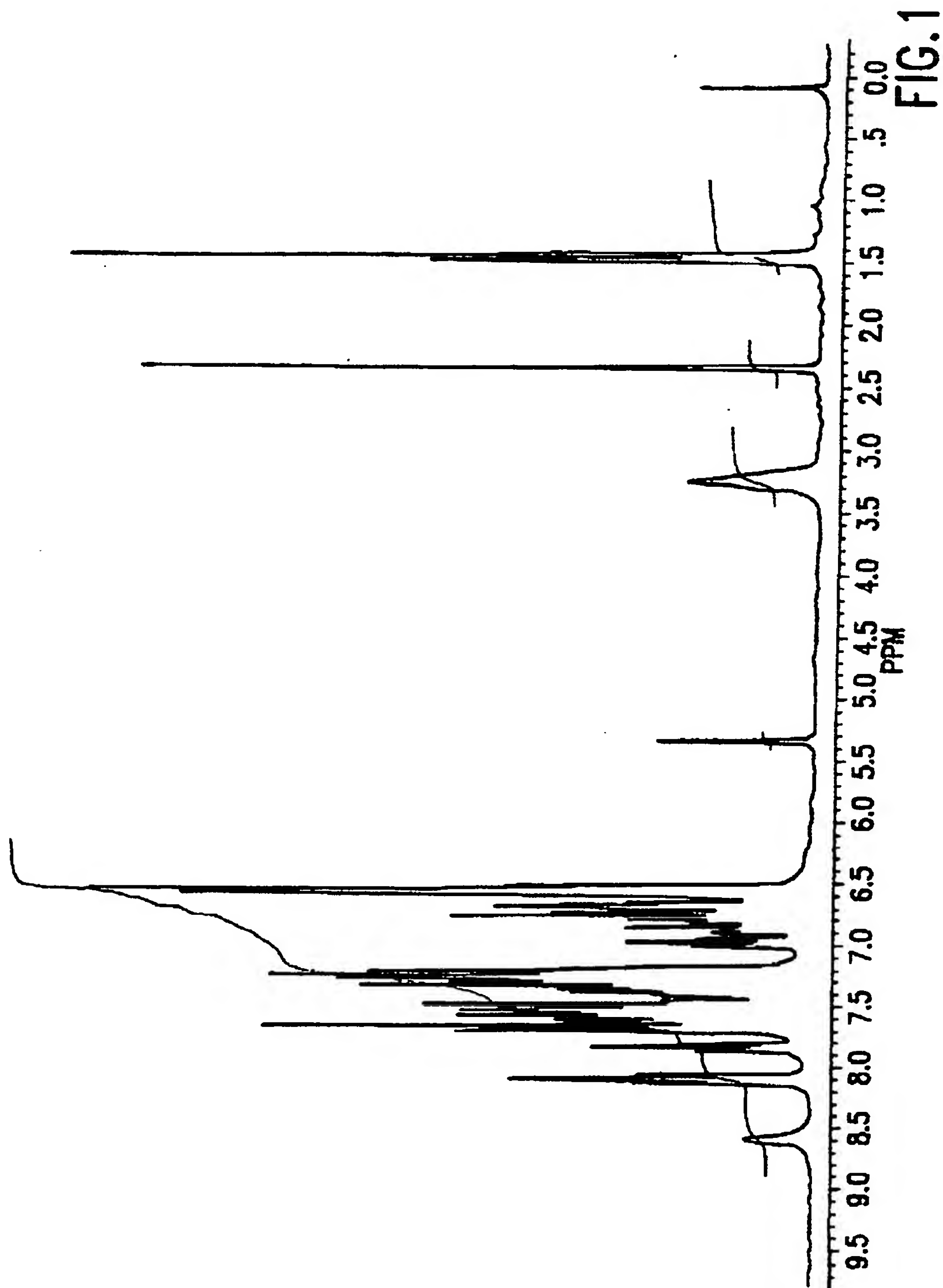
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1/2



2/2

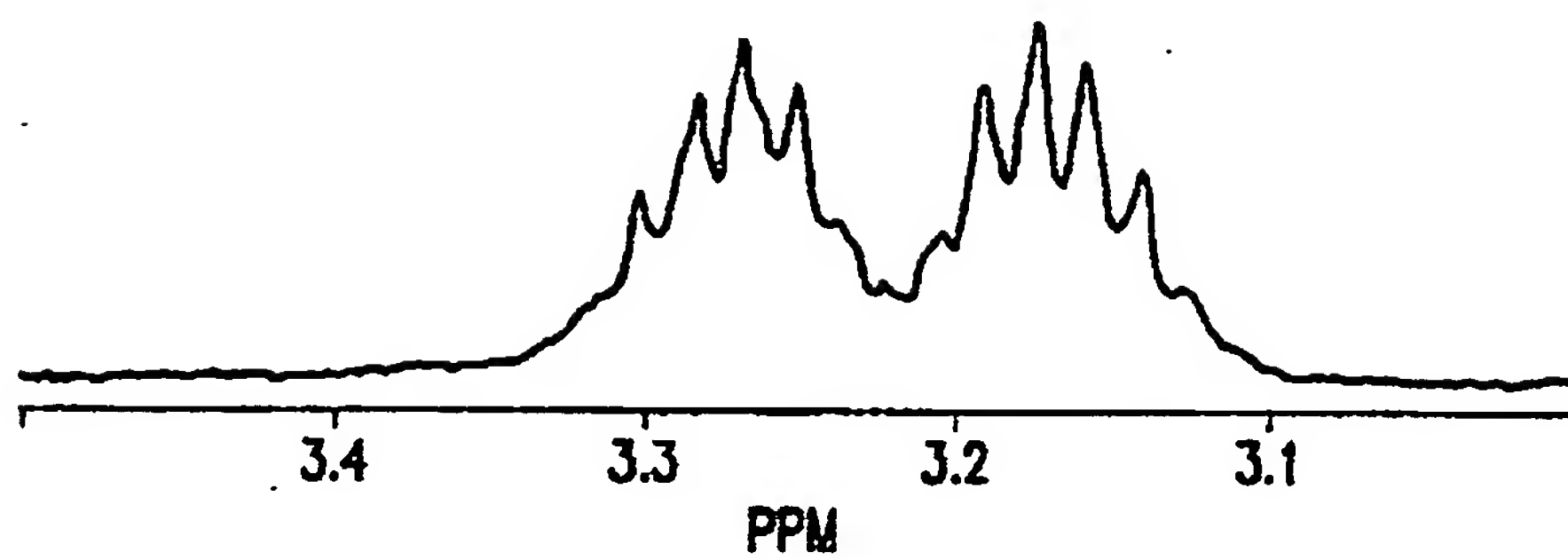


FIG. 2a

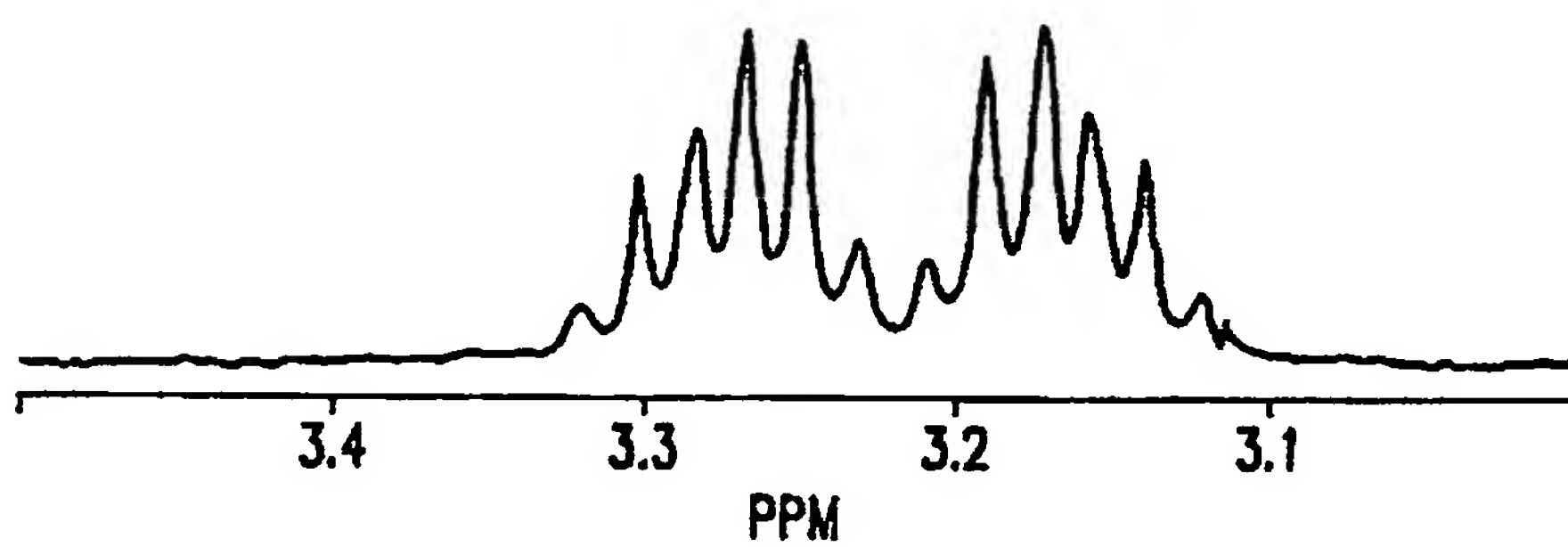


FIG. 2b

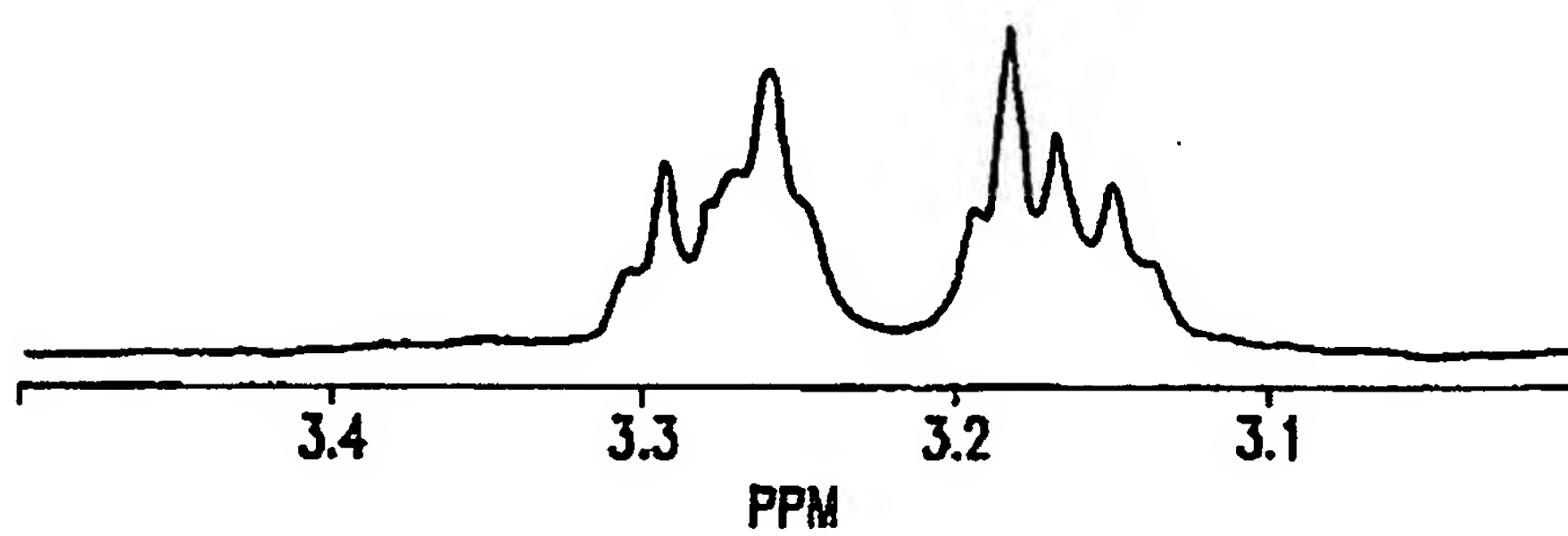


FIG. 2c

## INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/US 95/00117

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C67/31 C07C231/18 C07C69/675 C07F15/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0 295 109 (TAKASAGO INTERNATIONAL CORPORATION ) 14 December 1988 see page 2, line 26 - page 3, line 42 see page 4, line 20 - line 51 see page 5, line 12 - line 29 see page 5 - page 7; examples 1-17 see page 10 - page 11; claims -----	1-7, 11-21

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*B\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

24 April 1995

Date of mailing of the international search report

09.05.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Kinzinger, J

## INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 95/00117

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**EXAMPLES 1-3 DESCRIBE THE PREPARATION OF BINAP-RU COMPLEXES WITH DIETHYLAMINE FROM BINAP, A RU-COMPOUND AND TRIETHYLE AMINE. THESE COMPLEXES ARE CLAIMED IN 19 TO 21. ACCORDING TO THE STATE OF THE ART, THE PREPARATION OF EXAMPLES 1-3 FIELDS TRIETHYLAMINE COMPLEXES.**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**information on parent family members**

PCT/US 95/00117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-295109	14-12-88	JP-B- 6099367	07-12-94
		JP-A- 63310847	19-12-88
		DE-A- 3868700	09-04-92
		US-A- 4933482	12-06-90
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